Geiger & Associates

Geiger & Associates
3698 Gilroy Road
Salt Lake City, UT 84109
Phone 801.278.4334
Fax: 801.278.4212

Email: constancejgeiger@comcast.net

QUALIFIED HEALTH CLAIM PETITION

REDUCED RISK OF HEART DISEASE FROM CORN OIL AND CORN OIL-CONTAINING PRODUCTS

PART II

SUMMARY OF SCIENTIFIC DATA/EVIDENCE ANALYSIS

Prepared for
ACH Food Companies, Inc
7171 Goodlett Farms Parkway
Cordova, TN 38016-2927

By Constance J. Geiger, PhD, RD, CD

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Chapter 1

EXECUTIVE SUMMARY

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INTRODUCTION AND METHODOLOGY

This paper examines the scientific literature dealing with the effects of corn oil on coronary heart disease (CHD). Specifically, the evidence statements tested were 1) diets substituting corn oil for saturated fat may reduce the risk of CHD or 2) diets containing corn oil may reduce the risk of CHD.

Corn oil is composed of acylglycerols, primarily in the form of triglycerides. Polyunsaturated fatty acids (PUFAS) (predominantly linoleic acid) comprise the majority (59%) of the fatty acids in corn oil. Corn oil also contains 24% monounsaturated fatty acids (MUFAs) (oleic acid) and 13% saturated fatty acids (SFAs) (Dupont et al. 1990). Corn oil provides 136 mg of phytosterols and 2 IU vitamin E per 14 g, the Reference Amount Customarily Consumed (RACC) [United States Department of Agriculture (USDA) (2004)]. Used as a staple in the American diet since 1911, corn oil currently constitutes 7% of the fat consumption in the US [USDA Economic Research Service (ERS) 2004].

The Food and Drug Administration's (FDA 2003) Consumer Health Information for Better Nutrition Initiative's Task Force Final Report has provided guidance for an "Interim Evidence-Based Ranking System for Scientific Data." This system is being used to rate the evidence in this health claim petition.

FINDINGS

SCIENTIFIC AND PUBLIC NUTRITION POLICY DOCUMENTS

Virtually all scientific and public nutrition policy documents and reports support that diets containing PUFAs from vegetable oils or diets substituting unsaturated fat (PUFAs from vegetable oils) for saturated fat reduce blood cholesterol levels, thereby reducing the risk of CHD [United States Department of Health and Human Services (USDHHS) and USDA 2005; 2005 *Dietary Guidelines* Advisory Committee (2005 DGAC) 2004; FDA 2003; World Health Organization/Food and Agriculture Organization (WHO/FAO) 2003; Institute of Medicine (IOM) 2002, 2002/2005; National Cholesterol Education Program (NCEP) 2002; Krauss et al. 2000].

The Food and Nutrition Board, The IOM National Academy of Sciences Report on Dietary References Intakes: Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids (Macronutrient Report) (IOM 2002, 2002/2005) indicates that *n*-6 PUFAs positively affect blood lipid profiles, thus decreasing the risk of CHD.

> Interventional Evidence. *From the standpoint of blood lipids concentrations and CHD, higher n-6 polyunsaturated fatty acid intake generally alters blood lipid concentrations to result in a decreased risk profile (Katan et al., 1994) (Table 11-9). Controlled trials have examined the effects of substituting n-6 fatty acids in the diet to replace carbohydrate or saturated fatty acids (Mensink et al., 1992).... n-6 fatty acids decrease LDL cholesterol concentrations compared to saturated fatty acids (Mensink et al., 1992). (p. 821)*

A key recommendation of the *2005 Dietary Guidelines for Americans* (USDHHS and USDA 2005) emphasizes PUFAs from vegetable oils.

> *Keep total fat intake between 20 to 35 percent of calories, with most fats coming from sources of polyunsaturated and monounsaturated fatty acids, such as fish, nuts, and vegetable oils. (p. viii)*

Notably, the FDA Consumer Health Information for Better Nutrition Task Force Report on Qualified Health Claims (FDA 2003) mentions the importance of substituting vegetable oils for saturated fat to fight heart disease.

> *...Also, an increasingly important message for consumers is to substitute foods that decrease the risk of disease for those that do not, in order to build better diets. For instance, the booklet "Dietary Guidelines for Americans" provides an important substitution health message about fats and heart disease:*
>
> *"Substituting vegetable oils for solid fats may reduce your risk of heart disease."*
> *(2000 Dietary Guidelines for Americans, p. 7)*

The National Heart, Lung and Blood Institute's Expert Panel of the National Cholesterol Education Program (NCEP 2002) reports that elevated LDL cholesterol is a major cause of CHD. The following evidence statement supports the inclusion of linoleic acid in the diet and the substitution of PUFAs for SFAs to lower the risk of CHD:

> **Evidence Statements**
>
> *Linoleic acid, a polyunsaturated fatty acid, reduces LDL cholesterol levels when substituted for saturated fat acids in the diet....Controlled clinical trials indicated that substitution of polyunsaturated fatty acids for saturated fatty acids reduces risk for CHD.*

EVIDENCE-BASED RANKING SYSTEM

CORN OIL CONCLUSION STATEMENT

Virtually all papers in the evidence-based review support that 1) diets substituting corn oil for saturated fat may reduce the risk of CHD or 2) diets containing corn oil may reduce the risk of CHD. The effect of corn oil occurs through the lowering of total and low density lipoprotein (LDL) cholesterol and through the effect of naturally present phytosterols, which appear to bind cholesterol, thus making it unavailable for absorption into the body. The favorable fatty acid profile of corn oil, 59% PUFAs and 24% MUFAs, also contributes to its CHD benefit.

The rank is a "B" level health claim. **This rank is based on the following ratings: Quantity/Quality Rating ** or ***; Consistency ***; Relevance ***.**

OVERALL CONCLUSION

The information presented in this proposed health claim petition for corn oil and CHD fulfills the requirements for a "B" level health claim First, the results of the evidence-based ranking system demonstrate that the totality of the publicly available evidence supports that substituting corn oil for saturated fat lowers total and LDL cholesterol, thereby reducing the risk of CHD. Second, SSA exists among qualified experts that the relationship (PUFAs lowering total and LDL cholesterol, thereby reducing the risk of CHD) is valid as evidenced by the *2005 Dietary Guidelines* Committee Advisory Committee Report (2005 DGAC 2004); the *2005 Dietary Guidelines for Americans* (USDHHS and USDA 2005); the AHA Scientific Statement (Krauss et al. 2000); the Macronutrient Report (IOM 2002, 2002/2005); the WHO/FAO Report (2003); and the National Heart, Lung and Blood Institute's (NHLBI) Expert Panel of the National Cholesterol Education Program in the Adult Treatment Panel III Report (NCEP 2002). Furthermore, FDA (1999) has stated that SSA is met when the validity of a substance/disease relationship is not likely to be reversed by new and evolving science, although the exact nature of the relationship may need to be refined over time. For almost 50 years, research results have remained constant concerning the positive effect of corn oil on CHD through the lowering of total and LDL cholesterol. There is no reasonable scientific likelihood that this relationship will be reversed by new and evolving science.

Chapter

2 METHODOLOGY

Corn Oil and CHD:

Evidence Analysis

INTRODUCTION

The section provides background information about the purpose and progression of this evidence analysis. Cardiovascular disease (CVD) has been and continues to be the primary cause of death in the United States (AHA 2005, 2006). CHD is considered a type of CVD (AHA 2005, 2006) and in 2003 was the underlying or contributing cause of 58% of deaths (AHA 2006). CHD direct and indirect costs are estimated to be $142.5 billion in 2006, and CVD direct and indirect costs are estimated to exceed $430 billion (AHA 2006). Dietary and lifestyle changes can contribute to a reduced risk of CHD.

This paper examines the scientific literature on the effects of corn oil, a vegetable oil containing PUFAs, MUFAs and phytosterols, on CHD. Specifically, the evidence statements tested were 1) diets substituting corn oil for saturated fat may reduce the risk of CHD or 2) diets containing corn oil may reduce the risk of CHD.

In the MUFAs from Olive Oil and CHD letter (FDA 2004),

> *FDA identified the following endpoints to use in identifying CHD risk reduction for evaluating a health claim petition: coronary events (MI, ischemia), cardiovascular death, atherosclerosis, high blood pressure, serum total cholesterol, and serum LDL-cholesterol. High blood pressure, serum total cholesterol, and serum LDL-cholesterol levels are considered surrogate endpoints for CHD. Low HDL-cholesterol levels are considered a risk factor for CHD (NIH Consensus Conference, 1993). Atherosclerosis is the underlying cause of CHD, which can lead to the signs of CHD including coronary events (MI, ischemia) and cardiovascular death, high blood pressure, serum total cholesterol, and serum LDL- cholesterol.*

To evaluate the potential effects of corn oil on CHD risk, this evidence analysis examined blood lipids: serum total, LDL and high density lipoprotein (HDL) cholesterol.

The paper progresses by first describing the methodology for the evidence-based review (Chapter 2), and then reviewing the numerous scientific and public policy documents that discuss lipid recommendations (Chapter 3). The evidence-based review for corn oil is presented in Chapter 4. Chapter 5 contains the references. Appendices A-S are bound in a separate volume.

EVIDENCE-BASED RANKING SYSTEM FOR SCIENTIFIC DATA

The Food and Drug Administration's Consumer Health Information for Better Nutrition Initiative's Task Force Final Report (FDA 2003) provided guidance for an "Interim Evidence-Based Ranking System for Scientific Data." This system is being used to rate the evidence for this health claim petition.

An evidence-based ranking system is a science-based systematic evaluation of the strength of the evidence behind a statement, in this instance, the strength of the evidence supporting a substance/disease relationship. The process consists of 6 steps.

STEP 1: DEFINE THE SUBSTANCE/DISEASE RELATIONSHIP

This health claim petition tested 2 statements: 1) diets substituting corn oil for saturated fat may reduce the risk of CHD and 2) diets containing corn oil may reduce the risk of CHD.

STEP 2: IDENTIFY STUDIES THAT ARE RELEVANT TO THE SUBSTANCE/DISEASE RELATIONSHIP

All pertinent studies, primarily human, were collected and reviewed. The pertinent studies were found through MEDLINE and related searches.

We searched MEDLINE (no date limitations) to the present (January 30, 2006) for references to corn oil and cholesterol, corn oil and CVD and corn oil and CHD. The inclusion criteria were human studies and English language. The MEDLINE search for corn oil and CVD was included because AHA (2005, 2006) considers CHD as a type of CVD. Using CVD as a search term could provide some pertinent articles that would not be found in the corn oil and cholesterol and corn oil and CHD searches.

The MEDLINE searches were combined and duplicate articles were eliminated. One hundred fifty-nine articles were identified (see Appendix A). The abstracts, when available, were reviewed to determine the relevancy of the article. If an article was not reviewed, the rationale is noted (see Appendix A).

We included key animal citations by Rudel and colleagues and studies by Keys and Dayton recommended by experts in the field to be important in the substantiation of the role of PUFAs in progression of and death from CHD and important in predicting the role of PUFAs in blood lipids. We also included articles cited by the *2005 Dietary Guidelines* Advisory Committee Report (2005 DGAC 2004) and the Macronutrient Report (IOM 2002) intervention trials if they were not mentioned in the search.

STEP 3: CLASSIFY STUDIES BASED ON DESIGN TYPE

Each study is described by a design type. The experimental design is related to minimizing bias. Only those studies that include data collection are rated. These include:

- Design Type 1: Randomized, controlled, intervention trials
- Design Type 2: Prospective, observational, cohort studies
- Design Type 3: Nonrandomized, intervention trials with concurrent or historical controls and case-control studies
- Design Type 4: Cross-sectional studies, analyses of secondary disease endpoints in intervention trials and case series.

Reviews are not included in the rating system, but they may provide background information.

STEP 4: RATE EACH STUDY FOR QUALITY

Each study is independently reviewed and rated with a +, ø, - or NA. The rating is based on a sequence of questions that address relevance and methodological validity (see Appendix B for the "Quality Criteria Checklist: Primary Research" and "Quality Criteria Checklist: Review Article"). The relevance questions ask about the relevance of the research question to nutrition practice, the relationship of the study to the health of patients, the feasibility of the intervention and the importance of the outcome to patients. The validity questions include focus of the research question, methodology for subject selection, study group comparability, presence of blinding, reporting of subject withdrawal, details about study protocols, reliability and validity of the outcome measures, appropriateness of the statistical analyses, appropriateness of the conclusion and presence of bias due to funding source or sponsorship.

- \+ means the report has adequately addressed issues of scientific quality, such as sample inclusion/exclusion criteria, bias, generalizability and data collection and analyses
- ø means some uncertainties exist as to whether the report has adequately addressed the issues of scientific quality mentioned above
- – means the report has not adequately addressed issues of scientific quality
- NA means the report is not a primary reference; therefore, the quality has not been assessed.

All pertinent studies were evaluated and presented in evidence tables. The evidence tables are a summary of the significant components from each research article. This information includes study design, study rating for quality, sample size, sample characteristics (inclusion and exclusion factors), methodology, study duration, dietary intake, dietary assessment measures, amount of corn oil or PUFAs, results [*P* values, relative risk (RR) and hazard ratio (HR) values], author's conclusion and reviewer's comments, when appropriate.

The evidence analyses are presented by design type and are found in Appendices C through Q. The corn oil and CHD evidence tables are found in Appendices D through K. The PUFAs and CHD/CVD evidence tables are contained in Appendices L through Q. See Chapter 6 for a listing of the appendices.

The responses to the "Quality Criteria Checklist: Primary Research" or "Quality Criteria Checklist: Review Article" for each study are found on the tally sheets that appear in front of each evidence analysis table.

STEP 5: RATE THE STRENGTH OF THE TOTAL BODY OF EVIDENCE

All the studies then are considered as a group in order to rate the strength of the body of evidence. This rating system consists of 3 components: quantity/quality, consistency and relevance to disease risk reduction in the general population or in a target subgroup. Then the final ranking is assigned.

- Quantity/Quality: Takes into consideration the number of studies, the number of individuals studied and the generalizability of the findings to the target population. Designations include:
    - (***) means the number of studies of Design Types 1 and 2 and participants is large enough to comfortably generalize to the target population
    - (**) means there are sufficient studies of Design Type 3 and higher of a moderate quality but uncertainties exist regarding generalizability
    - (*) means there are insufficient numbers of studies and participants to generalize.
- Consistency: Takes into consideration whether the results of studies are similar across and within study design types
    - (***) means consistent results are present for a satisfactory number of study Design Types 1 and 2. These studies should be of + quality
    - (**) means moderate consistency
    - (*) means the results are inconsistent.
- Relevance to Disease Risk Reduction: Relates to whether the magnitude of the risk-reduction effect in the target group is physiologically significant and achievable
    - (***) means the magnitude of effect is physiologically significant in study Design Types 1 and 2, which are of + quality
    - (**) means the effect may be meaningful (Design Type 3 studies or higher)
    - (*) means the effect is not likely to be meaningful or achievable.

Four levels of ranking are suggested from 1 (A) to 4 (D): 1 (A) being SSA and 4 (D) being an extremely low level of comfort among qualified scientists that the claimed relationship is scientifically valid.

STEP 6: REPORT THE RANK

This step involves the creation of a statement that discusses "the nature of the evidence and the rationale for linking a substance to a disease or health-related concision with a ranking as to the strength of the scientific evidence in support of that relationship" (FDA 2003, p. 6).

Chapter 3 SCIENTIFIC AND PUBLIC POLICY DOCUMENTS

Corn Oil and CHD:

Evidence Analysis

INTRODUCTION

Virtually all scientific and public policy documents support 1) diets substituting PUFAs from vegetable oils for saturated fat may reduce the risk of CHD or 2) diets containing PUFAs from vegetable oils may reduce the risk of CHD.

FDA

Most recently the Task Force on Consumer Health Information for Better Nutrition Report on Qualified Health Claims indicated they would be conducting an evidence-based analysis of the literature concerning the substitution of unsaturated fat for saturated fat (FDA 2003).

The Task Force Report concluded that substituting unsaturated fat for saturated fat is an important message to communicate to consumers. The Report cites the *2000 Dietary Guidelines for Americans* (USDA and USDHHS 2000) recommendation to substitute unsaturated fat for saturated fat.

> *In addition, there is the opportunity to expand health messages beyond qualified health claims to dietary guidance. Public health priorities dictate a need for federal agencies and other stakeholders to partner to find useful and understandable health messages about general food choices and dietary patterns. ... Also, an increasingly important message for consumers is to substitute foods that decrease the risk of disease for those that do not, in order to build better diets. FDA can seek opportunities, using existing well-recognized government recommendations and partnerships, to identify the appropriate messages about food substitutions. For instance, the booklet "Dietary Guidelines for Americans" provides an important substitution health message about fats and heart disease:*

"Substituting vegetable oils for solid fats may reduce your risk of heart disease." (p. 7)

In 1993, in response to the Nutrition Labeling and Education Act of 1990 (NLEA 1990), FDA published final regulations for a health claim for diets low in saturated fat and cholesterol reducing the risk of CHD (21 CFR§101.75). The Agency stated that there is SSA among qualified experts that diets low in saturated fat and cholesterol may reduce the risk of CHD.

In 2000, FDA also approved a health claim for plant sterol/stanol esters and CHD (21 CFR§101.83). FDA regulations allowed for the claim to be made despite the fact that the substance exceeds the fat disqualifying levels. FDA stated that high blood total and LDL cholesterol are major modifiable risk factors in the development of CHD. The Agency further stated that the scientific evidence established that including plant sterol/stanol esters in the diet helps to lower total and LDL cholesterol levels. A recent study (Ostlund et al. 2002) has concluded that the phytosterols naturally present in corn oil contribute to its cholesterol-lowering effect.

THE AMERICAN HEART ASSOCIATION

The American Heart Association (AHA) Dietary Guidelines (Krauss et al. 2000) recommend "limiting foods high in saturated fat and cholesterol; and substituting unsaturated fat from vegetables, fish, and legumes and nuts" to achieve and maintain a desirable blood cholesterol and lipoprotein profile (p. 2285). The AHA statement specifically mentions PUFAs and MUFAs (when substituted for SFAs) as dietary factors that lower LDL cholesterol. Reduction of LDL cholesterol levels is associated with lowering the risk of CHD (p. 2285).

THE USDHHS AND USDA 2005 DIETARY GUIDELINES FOR AMERICANS

The *2005 Dietary Guidelines for Americans* (USDHHS and USDA 2005) are science-based eating and physical activity advice for healthy Americans over the age of 2. The *Dietary Guidelines* have included a fat guideline since their first publication in 1980.

The *2005 Dietary Guidelines for Americans* key recommendations for fat include:

Keep total fat intake between 20 to 35 percent of calories, with most fats coming from sources of polyunsaturated and monounsaturated fatty acids, such as fish, nuts, and vegetable oil.

The fat chapter indicates that

Fats and oils are part of a healthful diet, but the type of fat makes a difference to heart health.... (p. 29)

High intakes of saturated fats, trans fats, and cholesterol increase the risk of unhealthy blood lipid levels, which, in turn, may increase the risk of coronary heart disease. (p. 30)

This guideline provides additional information:

.... To meet the total fat recommendation of 20 to 35 percent of calories, most dietary fats should come from sources of polyunsaturated and monounsaturated fatty acids. Sources of omega-6 polyunsaturated fatty acids are liquid vegetable oils, including soybean oil, corn oil, and safflower oil. (p. 30)

In the *Report of the Dietary Guidelines Advisory Committee on the Dietary Guidelines for Americans, 2005* (2005 DGAC 2004*)*, an evidence-based approach was used to answer questions about diet and health. For *n*-6 PUFAs, the Committee asked

QUESTION 5:

What are the relationships between n-6 PUFA intake and health?

CONCLUSION:

An n-6 PUFA intake between 5 to 10 percent of energy may confer beneficial effects on coronary artery disease mortality. (p. 20)

The rationale for this recommendation was based on the Macronutrient Report's Acceptable Macronutrient Distribution Ranges (AMDRs) for *n*-6 PUFAs, the Macronutrient Report's evidence that supported beneficial effects of *n*-6 PUFAs on coronary disease mortality (IOM 2002, 2002/2005) and a systematic review of 17 papers (2005 DGAC 2004).

THE INSTITUTE OF MEDICINE

The Food and Nutrition Board, The Institute of Medicine National Academy of Sciences Report on Dietary References Intakes: Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids (Macronutrient Report) (IOM 2002, 2002/2005) discusses the associations among *n*-6 PUFAs, blood lipids and CHD. The report indicates that *n*-6 PUFAs positively affect blood lipid profiles, thus decreasing the risk for CHD.

Interventional Evidence. *From the standpoint of blood lipids concentrations and CHD, higher n-6 polyunsaturated fatty acid intake generally alters blood lipid concentrations to result in a decreased risk profile (Katan et al., 1994) (Table 11-9). Controlled trials have examined the effects of substituting n-6 fatty acids in the diet to replace carbohydrate or saturated fatty acids (Mensink et al., 1992). In general, any fat that replaces carbohydrate in the diet raises high-density lipoprotein (HDL) cholesterol and decreases triacylglycerols concentrations, with only small differences between fats. n-6 Fatty acids* *decrease LDL cholesterol concentrations compared to saturated fatty acids (Mensink et al., 1992). (p. 821)*

The Macronutrient Report also states that the epidemiological evidence supports the relationship between high intakes of *n*-6 PUFAs and a lower risk of CHD (IOM 2002/2005).

However, high intakes of n-6 polyunsaturated fats have been associated with blood lipid profiles (e.g., reduced total and low-density lipoprotein (LDL) cholesterol, reduced triacylglycerol, and increased high-density HDL cholesterol concentrations) that are associated with a low risk of coronary heart disease (CHD) (Arntzenius et al., 1985; Becker et al., 1983; Sonnenberg et al., 1996). Prospective epidemiological evidence suggests that after controlling for other components of the diets, replacing saturated fats with unsaturated fats decreases the risk of CHD (Hu et al., 1997).(p. 820)

THE NATIONAL CHOLESTEROL EDUCATION PROGRAM

The National Heart, Lung and Blood Institute's Expert Panel of the National Cholesterol Education Program (NCEP 2002) reports that elevated LDL cholesterol is a major cause of CHD. The Expert Panel recommends that intakes of saturated fat and cholesterol be reduced for primary prevention of CHD. The Panel also recommends a multifaceted lifestyle approach to reduce the risk for CHD that involves therapeutic lifestyle changes (TLC). The TLC diet recommends up to 10% of total calories from PUFAs. The rationale for this recommendation is based on the following evidence statements.

Evidence Statements

Linoleic acid, a polyunsaturated fatty acid, reduces LDL cholesterol levels when substituted for saturated fat acids in the diet. Polyunsaturated fatty acids also can cause small reductions in HDL cholesterol when compared with monounsaturated fatty acids, especially when present in high amounts in the diet. Controlled clinical trials indicated that substitution of polyunsaturated fatty acids for saturated fatty acids reduces risk for CHD.

Recommendation

Polyunsaturated fatty acids are one form of unsaturated fatty acids that can replace saturated fat. Most polyunsaturated fatty acids should be derived from liquid vegetable oils, semi-liquid margarines, and other margarines low in trans fatty acids. Intake of polyunsaturated fat can range up to 10 percent of total calories. (p. V-11)

Furthermore, the Expert Panel indicates that PUFAs usually result in a slightly greater reduction in LDL cholesterol levels than cis-MUFAs.

WORLD HEALTH ORGANIZATION (WHO)/FOOD AND AGRICULTURE ORGANIZATION (FAO) REPORT

The 2003 joint WHO/FAO report, Diet, Nutrition and the Prevention of Chronic Disease, addresses the strength of the evidence for preventing chronic diseases, including CHD. The WHO/FAO review classified the evidence as "convincing," which is their strongest rating, for linoleic acid decreasing the risk of CVD (WHO/FAO 2003).

The relationship between dietary fat and CVD, especially coronary heart disease, has been extensively investigated, with strong and consistent association emerging from a wide body of evidence accrued from animal experiments, as well as observational studies, clinical trials and metabolic studies conducted in diverse human populations (2). (p. 82)

When substituted for saturated fatty acids in metabolic studies, both monounsaturated fatty acids and n-6 polyunsaturated fatty acids lower plasma total and LDL cholesterol concentrations (10): PUFAs are somewhat more effective than monounsaturates in this respect.... The most important polyunsaturated fatty acid is linoleic acid, which is abundant especially in soybean and sunflower oils.... (p. 83)

Disease–specific recommendations: Diets should provide an adequate intake of PUFAs, i.e., in the range 6-10% of energy intake. There should also be an optimal balance between intake of n-6 PUFAs and n-3 PUFAs, i.e., 5-8% and 1-2% of daily energy intake, respectively. (p. 89)

Chapter

4 FINDINGS

Corn Oil and CHD:

Evidence Analysis

FINDINGS OF THE EVIDENCE-BASED RANKING SYSTEM: CORN OIL AND CHD

OVERVIEW OF CHAPTER 4

This chapter includes the results of the evidence-based ranking system for corn oil and CHD. Additional evidence summaries are included for PUFAs and CHD/CVD. These sections are followed by two sections that provide additional scientific information for the corn oil and CHD health claim petition: "Required Scientific Summary Issues to be Addressed" and "SSA Requirements."

STEP 1: EVIDENCE STATEMENT

The evidence statements tested were 1) diets substituting corn oil for saturated fat may reduce the risk of CHD and 2) diets containing corn oil may reduce the risk of CHD.

STEP 2: RESULTS OF LITERATURE SEARCH

The combined corn oil MEDLINE searches produced 159 articles for consideration (see Appendix A). The searches produced 43 articles eligible for review: 20 Type 1 Randomized, controlled, intervention trials; 0 Type 2 Prospective, observational, cohort studies; 17 Design Type 3 Nonrandomized, intervention trials with concurrent or historical controls and case-control studies; 2 Design Type 4 Cross-sectional studies, analyses of secondary disease endpoints in intervention trials and case series; 0 meta-analyses; 0 systematic reviews; 1 other review; and 3 animal studies. The remaining papers did not apply because they dealt with diseases or conditions other than heart disease, e.g., renal disease, dialysis, hypertension and cancer. The fish oil and omega-3 fatty acid studies used corn oil as a control. The studies were not included in the evidence analysis due to FDA's stance reported in the MUFAs from Olive Oil and CHD letter: "The studies were designed to determine if fish oils were beneficial to heart disease with olive oil used as a control source (not an intervention) and therefore lacked an adequate control for olive oil" (FDA 2004 p. 6). The fish oil and omega-3 fatty acid studies used corn oil in the same manner and therefore were not included in the evidence analysis.

Other studies found in the MEDLINE searches that related to mechanism of action of corn oil were analyzed but not included in the quantity/quality, consistency and relevance ratings for corn oil and CHD. These 3 other areas have separate evidence summaries without an overall rating: effects of phytosterols (found in corn oil), effects of corn oil on atherogenicity and effects of corn oil on postprandial lipids.

Design Type 1 PUFA studies cited by the Macronutrient Report (IOM 2002, 2002/2005) and Design Types 2, 3 and 4 studies cited by the *2005 Dietary Guidelines* Advisory Committee Report (2005 DGAC 2004) were reviewed if they were not covered in the search. Also included are key animal citations by Rudel and colleagues and studies by Keys and Dayton recommended by experts in the field to be important in the substantiation of the role of PUFAs in progression of and death from CHD and important in predicting the role of PUFAs on blood lipid levels. These studies were not included in the quantity/quality, consistency and relevance ratings for corn oil and CHD. They were analyzed to provide support for the role of PUFAs from corn oil in reducing the risk of CHD.

STEPS 3 TO 5: EVIDENCE SUMMARY CORN OIL AND BLOOD LIPIDS

This evidence summary discusses the effects of corn oil on serum total and LDL cholesterol, which are considered surrogate endpoints for CHD by FDA. The summary is divided into the 3 rating areas (quantity/quality, consistency and relevance). Each of these sections may be further subdivided into studies on healthy persons and healthy persons with high blood cholesterol levels or existing CHD.

STEP 6: CONCLUSION STATEMENT

Almost all the studies support that 1) diets substituting corn oil for saturated fat may reduce the risk of CHD or 2) diets containing corn oil may reduce the risk of CHD. The effect of corn oil occurs through the lowering of serum total and LDL cholesterol and through the effect of naturally present phytosterols that appear to bind cholesterol, thus making it unavailable for absorption into the body. The favorable fatty acid profile of corn oil, 59% PUFAs and 24% MUFAs, also contributes to its CHD benefit.

The rank is a "B" level claim. This rank is based on the following ratings: Quantity/Quality Rating ** or *; Consistency ***; Relevance ***.**

The supporting evidence for each of these ratings follows.

*QUANTITY/QUALITY RATING ** OR ****

In the reviewer's opinion, the number of studies examining the effects of corn oil on total and/or LDL cholesterol and CHD outcomes is good in both healthy subjects and in those with high blood cholesterol. Note: High total cholesterol and high LDL cholesterol are defined using the ATP III report definitions: $\geq$ 240 mg/dL ($\geq$ 6.24 mmol/L) and $\geq$ 160 mg/dL ($\geq$ 4.14 mmol/L), respectively (NCEP 2002).

Thirty-seven studies were reviewed: 20 Design Type 1 Randomized, controlled intervention trials (RCTS) (16 in healthy subjects, 2 in subjects with high blood cholesterol and 2 in subjects with a history of MI) and 17 Design Type 3 Nonrandomized, intervention trials. The quality is also good, with 83% (30 of 36) of rated studies being of "+" or "Ø" quality. (Note: 1 Design Type 3 study was noted as NA and not rated.) The studies are of strong design and are well-controlled to prevent bias (see Table 1).

All 16 (100%) Design Type 1 Randomized, controlled, intervention trials (RCTs) of healthy people are of "+" or "Ø" quality. In subjects with high blood lipids, both studies (100%) are of "+" quality. Both studies conducted with myocardial infarction (MI) subjects were rated as "Ø" quality. Ten of 16 rated (63%) Design Type 3 Nonrandomized, intervention trials are of "+" or "Ø" quality. All of those with lower ratings were conducted prior to 1970.

[Note: Five Design Type I RCTS (Lichtenstein et al. 1993a; Lichtenstein et al. 1993b; Lichtenstein et al. 1994a; Jones et al. 1994; Schwab et al. 1998) were conducted with a similar sample of middle-aged and elderly moderately hypercholesterolemic subjects with comparable protocols to Lichtenstein et al. (1994b). Therefore, subtracting these studies reduces the number of Design Type 1 RCTs on healthy subjects from 16 to 11 and the number of subjects from 1207 to 1135. All 16 Design I RCTs in healthy subjects are included in the Evidence Analysis because 1) the studies reported different findings, such as corn oil vs. baseline, corn oil vs. beef tallow, corn oil vs. olive oil and corn oil vs. corn oil margarine, and 2) the numbers of subjects completed varied between 14 and 15. In order to discuss the results, each paper was cited accordingly.]

When taking the similarity of the Design Type I studies into consideration and the 1 Design Type 3 study considered NA, a net of 15 Design Type I and 16 Design Type 3 studies were reviewed for a total of 31 studies. Of these, 80.6 % (25 of 31) were rated as being of "+" or "Ø" quality..

Design Type 1: Randomized, Controlled, Intervention Trials

Twenty Design Type 1 studies were reviewed: 16 in healthy subjects, 2 in subjects with high blood cholesterol and 2 in subjects with a history of MI (see Appendix D Evidence Table and Tally Sheet). [Note: A number of studies (Lichtenstein et al. 1993a; Lichtenstein et al. 1993b; Lichtenstein et al. 1994a; Jones et al. 1994; Schwab et al. 1998) were conducted with a similar sample of healthy, middle-aged and elderly moderately hypercholesterolemic subjects with comparable protocols to Lichtenstein et al. (1994b). Therefore, subtracting these studies changes the number of Design Type 1 studies from 20 to 15 and the number of subjects from 1207 to 1135.

Healthy People

Sixteen Design Type 1 RCTs have been conducted with 1207 healthy people [Wagner et al. 2001 (N=28); Schwab et al. 2000 (N=13); Howell et al. 1998 (N=16); Schwab et al. 1998 (N=14); Insull et al. 1994 (N=61); Jones et al. 1994 (N=15); Lichtenstein et al. 1994a (N=15); Lichtenstein et al. 1994b (N=14); Lichtenstein et al. 1993a (N=14); Lichtenstein et al. 1993b (N=14); Ng et al. 1991 (N=80); Wardlaw and Snook 1990 (N=20); Kohlmeier et al. 1988 (N=15); Laine et al. 1982 (N=24); Childs et al. 1981 (N=18); Dayton et al. 1969 (N=846)]. In most of these studies, corn oil and/or corn oil margarine was substituted for butter or beef tallow or compared to other oils.

Twelve are of "+" quality (Wagner et al. 2001; Howell et al. 1998; Insull et al. 1994; Jones et al. 1994; Lichtenstein et al. 1994a; Lichtenstein et al. 1994b; Lichtenstein et al. 1993a;

TABLE 1. SUMMARY TABLE OF STUDIES

STUDY DESIGN TYPE*	STUDY TYPE DESCRIPTION	TOTAL STUDIES # (NET)**	STUDIES ON HEALTHY SUBJECTS # (NET)**				STUDIES ON SUBJECTS WITH CHD OR HIGH BLOOD CHOLESTEROL #			
		[Total # of Subj, Net]	Quality Rating #				Quality Rating #			
			"+"	"Ø"	"-"	NA	"+"	"Ø"	"-"	NA
1	Randomized, controlled, intervention trials	20(15) [1411, 1339]	12(8)	4 (3)	0	0	2	2	-	-
2	Prospective observational cohort studies	0	-	-	-	-	-	-	-	-
3	Nonrandomized intervention trials with concurrent or historical controls and case-control studies	17(16) [310, 304]	5	3, 1 "Ø" /"-"	4	1		2	1	-
4	Cross-sectional studies, analyses of secondary disease endpoints in intervention trials and case series	2 (0)	-	-	-	1	-	-	-	1
	Meta-analyses	0	-	-	-	-	-	-	-	-
	Systemic reviews	0	-	-	-	-	-	-	-	-
	Other reviews	1 (0)	-	-	-	-	-	-	-	1
	Animal studies	3	1	-	1	1	-	-	-	-

* See Chapter 2 for more detailed information on the methodology

**Six Design Type 1 studies were conducted on largely the same group of subjects but were reported separately because they reported different findings. If those 6 studies were consolidated and considered as a single study, the numbers would be as shown in parentheses, the net number. For other types of studies, the net number reflects the subtraction of the NA studies

Lichtenstein et al. 1993b; Ng et al. 1991; Wardlaw and Snook 1990; Kohlmeier et al. 1988; Dayton et al. 1969); and 4 are of "Ø" quality (Schwab et al. 2000; Schwab et al. 1998; Laine et al. 1982; Childs et al. 1981). (Note: Hiscock et al. 1962 described the diet used for the Dayton et al. 1969 study.)

Subjects with High Blood Cholesterol Levels or Existing CHD

Two Design Type 1 RCTs have been conducted in 35 subjects with high blood cholesterol levels [Sirtori et al. 1992 (N=12); Sirtori et al. 1986 (N=23)] and 2 (N=169) were conducted in persons with an MI [Grundt et al. 2004 (N= 273 TX—started with 300; 89 follow-up); Rose et al. 1965 (N=80) ischemic heart disease (IHD) patients]. Two were rated of "+" quality (Sirtori et al. 1992; Sirtori et al. 1986); and 2 of "Ø" quality (Grundt et al. 2004; Rose et al. 1965).

Design Type 2: Prospective, Observational, Cohort Studies

No cohort studies have been conducted using corn oil.

Design Type 3: Nonrandomized, Intervention Trials with Concurrent or Historical Controls and Case-Control Studies

Seventeen Design Type 3 Nonrandomized, intervention trials were conducted in healthy people (14 studies) and in subjects with high blood cholesterol levels or with existing CHD (3 studies) (see Appendix E Evidence Table and Tally Sheet). (Note: 1 Design Type 3 study was noted as NA and not rated, therefore a net of 16 Design Type 3 studies were rated.) (See Table 1.)

Healthy Subjects

Fourteen nonrandomized, intervention trials have been conducted with 251 healthy people [Cuchel et al. 1996 (N=14); Imaki et al. 1989 (N=4); Mitchell et al. 1989 (N= 6); Zanni et al. 1987 (N=9); Snook et al. 1985 (N=12); Fisher et al. 1983 (N=9); Chance et al. 1969 (N=34); Kaplan et al. 1965 (N=8); Haust and Beveridge 1963 (N=2); Lloyd et al. 1962 (N=31); Kingsbury et al. 1961 (N=11); Horlick 1959 (N=6); Grande et al. 1958 (N=93); Engelberg 1957(N=12)].

Five studies are rated "+" (Cuchel et al. 1996; Imaki et al. 1989; Zanni et al. 1987; Snook et al. 1985; Fisher et al. 1983); 3 are rated "Ø" (Kaplan et al. 1965; Kingsbury et al. 1961; Grande et al. 1958); 1 is rated "Ø/-" (Lloyd et al. 1962); 4 are rated "-" (Chance et al. 1969; Haust and Beveridge 1963; Horlick 1959; Engelberg 1957); and 1 is NA (Mitchell et al. 1989). Subtracting the subjects in the Mitchell et al. 1989 study rated NA results in a net of 245 healthy subjects.

Subjects with High Blood Cholesterol Levels or Existing CHD

Three studies were conducted in subjects with high blood cholesterol levels or with existing CHD (N= 59). One "Ø" rated study was conducted with 8 subjects having high blood cholesterol levels [Rhoads and Barker 1959 (N=8)]. One Ø" rated study [Watson 1963 (N=28)] and 1 "-" rated study [Tobian and Tuna 1958 (N=23)] were conducted in men who had an MI.

Design Type 4: Cross-Sectional Studies, Analyses of Secondary Disease Endpoints in Intervention Trials and Case Series

Two case series/reports have been conducted in healthy and hypercholesterolemic subjects [Albutt and Chance 1969 (N=34 healthy and hypercholesterolemic subjects) and Carlson and Sterner (1960) (N= 3 hypercholesterolemic subjects)]. Both were rated (NA) because very little information was available about the study design and subjects (see Appendix F Evidence Table and Tally Sheet).

Meta-Analyses and Systematic Reviews

No meta-analyses or systematic reviews have been conducted with corn oil. However, DuPont et al. (1990) conducted a nonsystematic review that was rated NA (see Appendix G Evidence Table and Tally Sheet).

Animal Studies

One Design Type 1 study of "+" quality was conducted with 50 male guinea pigs (Ramjiganesh et al. 2002). One "-" rated study was conducted with 40 White Rock cockerels (Anon 1958). One animal study was NA: Day (1960) (cellular study) (see Appendix H Evidence Table and Tally Sheet).

*CONSISTENCY ****

The consistency of the results is very strong regardless of the dose and the study design, which is remarkable. The size of the effect ranges from $P < .05$ to $P < .0001$.

The data from 19 of 20 (95%) of the "+" and "Ø" rated **Design Type 1** Randomized, controlled, intervention trials that examined the effect of corn oil on blood lipids with healthy subjects and those with high blood cholesterol levels or existing CHD consistently show that when corn oil replaces saturated fat or other oils or when corn oil is included in the diet, blood lipids are improved: Total and/or LDL cholesterol decreases (see Appendix D3, Table. Corn Oil Design Type I Studies: Postintervention Blood Lipid Concentrations). Subtracting the similar studies by the Lichtenstein group changes this number to 14 of 15 (93%).

HDL remains unchanged (Wagner et al. 2001; Howell et al. 1998; Wardlaw and Snook 1990; Kohlmeier et al. 1988; Schwab et al. 1998; Laine et al. 1982; Childs et al. 1981), increases (Grundt et al. 2004; Schwab et al. 2000) or in a few cases decreases (Schwab et al. 2000; Insull et al. 1994; Jones et al. 1994; Lichtenstein 1994b; Lichtenstein 1993a; Lichtenstein 1993b; Ng et al. 1991). In most of these studies, if HDL decreases it does so in the face of an LDL or total cholesterol decrease, resulting in the LDL/HDL or total cholesterol/HDL ratio remaining the same or improving. In 1 study in subjects with Type II hypercholesterolemia, blood cholesterol levels were not significantly different from the baseline prudent diet, which contained less than 10% calories from saturated fat and 30-32% calories from total fat (Sirtori et al. 1992).

The findings from all but 1 **Design Type 3** Nonrandomized, intervention trials that examined the effect of corn oil on blood lipids with healthy subjects and those with high blood cholesterol levels or existing CHD consistently show that when corn oil replaces saturated fat or when corn oil is included in the diet, blood lipids are affected favorably: total and/or LDL cholesterol decreases. In those studies that reported HDL cholesterol, it remains unchanged (Cuchel et al. 1996) or decreases (Imaki et al. 1989; Zanni et al. 1987; Snook et al. 1985; Fisher et al. 1983). If HDL decreases it does so in the face of an LDL or total cholesterol decrease, resulting in the LDL/HDL or total cholesterol/HDL ratio remaining the same or improving. The 1 study that showed no change in serum cholesterol levels was conducted in patients who had already been on a reduced fat diet for several years and had experienced a drop in total cholesterol. The addition of corn oil to this reduced fat diet did not reduce serum cholesterol levels further (Engelberg 1957). The reduced fat diet was characterized as being reduced in animal fat, containing 40 to 50 g of fat per day.

Three Design Type 1 studies and 2 Design Type 3 studies strongly suggest the effects of corn oil are also related to the effect of naturally present phytosterols, which appear to bind cholesterol, thus making it unavailable for absorption into the body (Ostlund et al. 2002; Kohlmeier et al. 1988; Howell et al. 1988; Haust and Beveridge 1963; Grande et al. 1958). In addition to the discussion of these studies below, see "Effect of Phytosterols," p. 30.

The studies are discussed in further detail below.

Design Type 1: Randomized, Controlled, Intervention Trials

Healthy Subjects

All 12 of the "+" quality Design Type 1 studies in healthy people report lowered serum total and/or LDL cholesterol when corn oil is consumed.

In a randomized, double-blind, crossover trial, Wagner et al. (2001) compared the effects of PUFAs as corn oil and MUFAs as an olive oil/sunflower oil mixture on plasma lipoproteins in 28 young, healthy males. The corn oil diet had a significantly greater effect on lipoprotein metabolism than did the MUFA mixture. Only the PUFA-rich corn oil diet significantly ($P < 0.01$) reduced LDL cholesterol after the first test period compared to the baseline diet. Furthermore, the PUFA-rich corn oil diet significantly ($P < 0.01$) lowered total cholesterol (after the second treatment period) and significantly lowered ($P < 0.05$) total triglycerides and ($P < 0.01$) VLDL-TG after the first treatment period over the MUFA-mixed oil diet. Notably this effect was significant after 2 weeks of treatment. HDL levels were not significantly different between groups or test periods.

Using a randomized Latin-square design, Howell et al. (1998) examined the effect of 3 treatments–corn oil, olive oil and olive oil enriched with phytosterols–on plasma lipids in 16 normolipidemic subjects. Each treatment lasted 10 days, separated by a washout period of 2 weeks of an ad libitum diet prior to the next treatment. All meals were prepared and consumed in a metabolic unit. The corn oil diet contained a mean of .63 g phytosterols/1000 kcal and the enriched olive oil diet contained 1.45 g/1000 kcal. Total cholesterol concentrations were significantly higher ($P = 0.001$) after both olive oil and olive oil + phytosterol diets (3.71 $\pm$ 0.15 mmol/L; 3.65 $\pm$ 0.13 mmol/L) over the corn oil diet (3.32 $\pm$ 0.11 mmol/L). The olive oil diet resulted in a significantly higher ($P < 0.05$) LDL cholesterol level (2.17 $\pm$ 0.12 mmol/L) than did corn oil (1.99 $\pm$ 0.12 mmol/L). HDL levels were not significantly different among the 3 treatments. When phytosterols were added to olive oil, there was no difference in LDL cholesterol between this diet and the corn oil diet. The authors concluded that the phytosterols naturally present in corn oil contributed to the differences among the treatments.

In 61 healthy, free-living people consuming partially hydrogenated corn oil, soybean or sunflower oil (PUFAs at 6% of total energy) as part of a low fat (22-26% of energy) diet, Insull et al. (1994) found that all 3 diets lowered total cholesterol, LDL cholesterol and HDL cholesterol. Compared to the ad libitum diet, corn oil lowered total cholesterol (-11%) (*P* < 0.0001), LDL cholesterol (-12%) (*P* < 0.0001) and HDL cholesterol (-11%) (*P* < 0.0001). The amount of PUFAs in the corn oil diet was 16.7 g/2010 calories for men and 16 g/1549 calories for women. Triglyceride levels were not affected. The corn oil diet was administered for 5 weeks.

In 3 matched groups of healthy volunteers (N=80), Ng et al. (1991) examined the effects of diets enriched with corn oil, palm olein or coconut oil on serum lipids. After a run-in period, each group began the experiment with 5 weeks of coconut oil, followed by 5 weeks of corn, palm or coconut oil, ending with a third 5-week period of coconut oil. Ng et al. (1991) found that corn oil given as 75% of total fat (32% of calories) when compared to the first treatment period of coconut oil resulted in a significant lowering of total cholesterol (-36%) (*P* = 0.001), LDL cholesterol (-42%) (*P* < 0.001) and HDL cholesterol (-26%) (*P* < 0.001). Corn oil also significantly lowered TG (*P* = 0.01) when compared with the preceding coconut oil period or with concentrations at baseline (*P* = 0.02). The corn oil diet also significantly lowered total cholesterol (-29%) (*P* < 0.001) from baseline values.

In a randomized, controlled, crossover trial with a 7-week washout period between treatments, Wardlaw and Snook (1990) found that corn oil favorably affected blood lipid levels. Twenty healthy men were given diets for 5 weeks that substituted either corn oil or high oleic acid sunflower oil (HOSO) (85% of total fat) for saturated fat (85% of total fat)(butter) without lowering total fat (40% of kcal). Mean serum total cholesterol, LDL and TG on the corn oil diet were significantly reduced relative to the butter-based diet [-21% (*P* < 0.001), -26% (*P* < 0.001) and -21% (*P* < 0.01), respectively] and to baseline values (*P* < 0.05). HDL levels did not change. Furthermore, when corn was compared to the HOSO diet, corn oil lowered total cholesterol (*P* < 0.03) and LDL cholesterol (*P* < 0.04) more than did the HOSO diet. When the cholesterol was added to the corn oil diet to be equivalent to the butter diet, total, LDL and HDL cholesterol levels were not changed.

A number of studies (Lichtenstein et al. 1993a; Lichtenstein 1993b; Lichtenstein et al. 1994a; Jones et al. 1994; Schwab et al. 1998) were conducted with a similar sample of middle-aged and elderly moderately hypercholesterolemic subjects with comparable protocols. The diets contained two-thirds of dietary fat (20% of total energy) from 1 of a variety of oils (corn, canola, rice bran or olive oil), beef tallow or margarine as part of a diet that followed National Cholesterol Education Program Step 2 Guidelines. The studies examined individual effects of the oils on lowering plasma lipids levels and improving the cardiovascular risk profile. A baseline diet of 32 days was followed by varying oil-enriched diets, for 32 days each.

In the first study, Lichtenstein et al. (1993b) found significant reductions in plasma cholesterol after each of the test oil diets compared to baseline, with greater reductions for corn oil (-13 ± 6%, *P* = 0.001) than for olive oil (-7 ± 7%, *P* = 0.01). LDL cholesterol significantly decreased (*P* = 0.001) after all the test oil diets compared to baseline: corn (-17 ± 8%), canola (-16 ± 3%) and olive oil (-13 ± 8%). No differences in the decrease of LDL cholesterol existed among the oils. Although corn (-9 ± 7%) and canola (-7 ± 3%) both significantly decreased HDL (*P* = .01 and 0.05, respectively), there were no significant effects on the total/HDL cholesterol ratio.

Lichtenstein et al. (1993a), in the same group of subjects on the same diet protocols, compared the effect of hydrogenation on the hypolipidemic effect of corn oil. Both dietary treatments (corn oil and corn oil margarine) significantly decreased total, LDL and HDL cholesterol: total cholesterol [corn oil -13 ± 6% (*P* = 0.001); corn oil margarine -7 ± 10% (*P* = 0.006)]; LDL cholesterol [corn oil -17 ± 8% (*P* = 0.001); corn oil margarine -10 ± 12% (*P*

= 0.003)]; and HDL cholesterol [corn oil -9 ± 7% (P = 0.002); corn oil margarine -11 ± 9% (P = 0.002)]. The diet fortified with corn oil margarine was not as efficacious as the diet fortified with corn oil in reducing total cholesterol (P < .039), but it still improved blood lipids.

Lichtenstein et al. (1994b) examined the addition of two-thirds of the fat content of the diet as beef tallow (high in stearic acid) versus corn oil (high in PUFAs) in 14 middle-aged and elderly women and men. The corn oil diet significantly reduced total cholesterol (-13%; P < .05) and LDL cholesterol (-17%; P < .05), whereas the beef tallow did not reduce total cholesterol but did reduce LDL cholesterol (-8%; P < .05). Both diets reduced HDL compared to baseline (corn -9%; beef tallow -7%) (P < .05).

Lichtenstein et al. (1994a) compared rice bran oil to corn-, canola- and olive oil-enriched diets (administered for 32 days each) in 15 middle-aged to elderly men and women. Total and LDL concentrations/reductions were not significantly different among the corn-, canola- and rice bran oil-enriched interventions. However, corn oil as well as canola and rice bran oils produced greater reductions in total (P = 0.1) and LDL cholesterol (P = 0.01) than did the olive oil-enriched intervention. The groups did not vary with respect to their effects on VLDL, HDL, TAG, LDL apo B, apoA-1 and Lp(a), total cholesterol:HDL ratio and LDL apoB:apoA-1 ratios. The percent changes were not provided.

The Jones et al. (1994) study found differences in cholesterol synthesis among the 4 diets (baseline diet, olive, corn and canola) in 15 postmenopausal women. Their findings suggested that a more rapid flux of central-pool cholesterol is associated with increased synthesis after the corn oil-enriched diet versus the olive oil-enriched diet. This result suggests different mechanisms control circulating cholesterol levels, depending on the oil consumed; however, blood lipids are favorably affected. They also found differences in blood lipids when a corn oil diet providing two-thirds of the dietary fat (diet 30% calories from fat) was compared to the baseline diet of 35% of calories from fat (15% SFA, 15% MUFA, 6% PUFA). On the corn oil diet, total ($P \leq 0.005$), LDL ($P \leq 0.001$) and HDL ($P \leq 0.01$) cholesterol were significantly lower. Replacing saturated fat with corn oil had a favorable effect on blood lipids, e.g., lowered total and LDL cholesterol.

In a randomized, crossover trial with 4-week treatment and 6-week washout periods, Kohlmeier et al. (1988) found that 75 g of corn oil products significantly lowered total cholesterol (-25%) ($P \leq 0.001$) and LDL cholesterol (-29.3%) ($P \leq 0.001$) in 15 healthy men with higher than average cholesterol levels (5.2-6.7 mmol/L). This lipid lowering effect was significantly greater than with sunflower oil (P < .01). HDL levels were not changed. These subjects also had a significantly higher sterol excretion on the corn oil diet compared to that on an unrestricted normal diet ($P \leq .05$). Furthermore, Kohlmeier et al. (1988) demonstrated a strong inverse correlation between the change in serum cholesterol levels and the change in endogenous sterol excretion. The corn oil diet contained 35 g corn oil and 40 g of corn oil margarine.

In a landmark study, Dayton et al. (1969) found that when unsaturated fat was substituted for saturated fat in 846 elderly men for about 8 years, the treatment group had a 12.7% lower serum cholesterol level than the control group throughout the duration of the study. The linoleic acid content was 10% of total fatty acids in the control diet and 38% in the experimental diet. The vegetable oils used in order of decreasing quantity were corn, soybean, safflower and cottonseed. (Note: Additional dietary details were reported in Hiscock et al. 1962.)

All 4 "Ø" quality Design Type 1 studies reported significantly improved blood lipids. Schwab et al. (2000) and Schwab et al. (1998) found blood lipids higher with beef tallow than with corn oil, when 20% of the energy came from the respective fats. Two other studies showed corn oil lowered total and LDL cholesterol with no change in HDL (Laine et al. 1982; Childs et al. 1981).

Schwab et al. (2000) examined 13 moderately hypercholesterolemic subjects and found dietary cholesterol added to reduced fat diets high in PUFA from corn oil (20% of energy) or high in SFA in beef tallow raised blood lipid values over baseline values with the same oils. Schwab et al. (1998) found plasma total and LDL cholesterol levels were significantly ($P < .05$) higher after the beef tallow diet than after corn oil diets in 14 subjects. Total cholesterol following the beef tallow diet was 5.63 $\pm$ 0.79 mmol/L and after the corn oil diet was 5.05 $\pm$ 0.51 mmol/L. Plasma LDL cholesterol following the beef tallow diet was 3.62 $\pm$ 0.70 mmol/L and after the corn oil diet was 3.24 $\pm$ 0.49 mmol/L. HDL and triglyceride levels remained similar. Study periods were 32 days each followed by 32 days of washout on subjects' habitual diets.

Laine et al. (1982) compared corn, soybean, palm and lightly hydrogenated soybean oils in 24 young, healthy, college students. Those subjects consuming the corn oil diet showed significant decreases in total (-13.2%) and LDL cholesterol (-22.8%). Those students assigned to the unhydrogenated soy oil diet also experienced significant decreases in total and LDL cholesterol. Corn oil was more effective than lightly hydrogenated soybean oil in lowering ($P < .01$) both total and LDL cholesterol. HDL levels were not changed significantly with any of the diets, but TG showed significant ($P < .05$) small decreases with corn and the other nonhydrogenated oils but not with the lightly hydrogenated soy oil. The amount of PUFA from corn oil was analyzed at 53 g in 3000 calories. Daily corn oil intake ranged from 46 g at 1900 kcal to 77.5 g at 3500 kcal. Each study period was 20 days.

Childs et al. (1981) compared responses to the addition of 30.5 g of corn oil and 36 g of dietary soy lecithin to diets of 12 normolipidemic and 6 hypercholesterolemic subjects. Corn oil consistently and significantly lowered LDL-C by -12.3 $\pm$ 2.3% ($P < 0.002$) in normolipidemics and by -9.8 $\pm$ 1.5% in hyperlipidemics, with no effect on HDL-C. Total cholesterol also was significantly lowered in both groups: -8.4 $\pm$ 1.2% ($P < 0.002$) in normolipidemics and -6.2% + 1.5% ($P < 0.01$) in hypercholesterolemics. Triglycerides were not changed. The test periods were 3 weeks.

Subjects with High Blood Cholesterol or Existing CHD

Sirtori et al. (1992) found a prudent diet with 10% of calories from corn oil was the same as the baseline prudent diet with less than 10% of calories from SFA on blood lipids levels in 12 hypercholesterolemic patients. The baseline prudent diet was provided for 1 month prior to the 6-week treatment with corn oil. These results differed from their earlier study (Sirtori et al. 1986); however, two-thirds of the patients experienced decreased total and LDL cholesterol (-4.7 5 and 6.1%, respectively), 2 subjects experienced no changes and 2 had a slight increase.

Sirtori et al. (1986) found that diets rich in corn oil administered for 4 weeks significantly lowered total (-6.8 to -7.7%; $P < .05$) and LDL cholesterol (-6.9 to -9.2%; $P < .05$) versus a diet rich in olive oil in 23 middle-aged patients at high risk for atherosclerosis relative to baseline levels. HDL decreased significantly (-4.6%; $P < .05$) in 1 diet sequence, corn-olive, but was not significant after the olive-corn sequence. Importantly, the corn oil diet improved the LDL/HDL ratio from a baseline of 4.51 to 4.25.

In 1 "Ø" rated study, Grundt et al. (2004) compared dietary supplements of four, 1-g capsules of corn oil or 4 capsules of omega-3 fatty acids, each containing 850-882 mg of n-3 PUFAs added to the diet for 12 to 24 months in 300 patients who had an acute MI.

Patients were followed for 0-34 months after treatment cessation. In the corn oil group, total cholesterol decreased approximately -15% ($P < 0.001$) and HDL cholesterol increased +11% ($P = 0.05$) from baseline to 24 months. No other differences in blood lipids existed between the 2 groups.

In the second "Ø" rated study, Rose et al. (1965) examined 3 groups: 2 given corn oil or olive oil (80 g/day in equal doses at meal time) and 1 with no treatment (control). The 80 subjects were ischemic heart disease patients with a history of MI or angina. Rose et al. (1965) examined the effects of corn or olive oil on serum cholesterol levels and major cardiac events. The study was planned for 3 years, but by 2 years one-half of the subjects had died or were lost to follow-up. Total cholesterol significantly decreased from baseline for only the corn oil treatment, but not for the olive oil or the control group. Corn oil decreased cholesterol a mean of -25.5 ± 8.8 mg/100 mL at 6 months ($P < 0.01$) and maintained this drop through 18 months of study (-30.3 ± 9.9 mg/100 mL). By 2 years the mean change was -19.9 + 13.5 mg/100 mL ($P < 0.2$). After 2 years, the control group had more patients remaining free of major cardiac events (75%) than either the corn oil group (52%) or the olive oil group (57%), which approached significance ($0.1 > P > 0.05$). Notably, the oil intake of the control subjects was not assessed and a placebo was not used. Dietary intake was assessed only during the second year of follow-up and was collected only for one-half to two-thirds of subjects who began the study in each group—the other half had died or were lost to follow-up. The authors attempted to assess oil intake over time, and the estimated amounts (which were considered the maximum) consumed were 74 g a day at 6 months and 51 g/d at 24 months for corn oil; and 73 g per day at 6 months and 51 g per day at 24 months for olive oil. Again oil intake of the control group was not assessed. Based on the study limitations, it is difficult to determine if the change in cardiac events was due to the oil treatments.

Design Type 3: Nonrandomized, Intervention Trials with Concurrent or Historical Controls and Case-Control Studies

All "+" and "Ø" Design Type 3 studies in normolipidemic and subjects with high blood cholesterol levels showed significant reductions in total and/or LDL cholesterol when subjects consumed diets containing corn oil that replaced saturated fat or other oils (Cuchel et al. 1996; Imaki et al. 1989; Zanni et al. 1987; Snook et al. 1985; Fisher et al. 1983; Chance et al. 1969; Kaplan et al. 1965; Watson 1963; Kingsbury et al. 1961; Chance et al. 1969; Haust and Beveridge 1963; Grande et al. 1958).

Healthy Subjects

In a "+" rated Design Type 3 study, Cuchel et al. (1996) studied the effects of a corn oil-enriched diet (11% PUFA) versus a corn oil stick margarine-enriched diet (8% PUFA) on blood lipids and on susceptibility to oxidation in 14 middle-aged and elderly hypercholesterolemic subjects. The 32-day NCEP baseline diet was followed by 32 days of each treatment. Lipid values for total cholesterol were higher for the corn oil margarine than for the corn oil diet: total cholesterol ($P = 0.039$). LDL and HDL cholesterol were not significantly different. Both the corn oil- and the corn oil margarine-enriched diets decreased lipid levels over baseline values (see Lichtenstein et al. 1993a; Lichtenstein et al. 1993b).

In a metabolic ward study, Imaki et al. (1989) examined the effects of 30 g/day of lard versus 30 g of corn oil added to a basal diet for 7 days in 4 young Japanese men. The treatments were consecutive. After 7 days, lard significantly increased total cholesterol from baseline [106 ± 23 mg/dl to 141 ± 26 mg/dl ($P < .05$)] and corn oil significantly decreased total cholesterol from the lard treatment (141 ± 26 mg/dl to 111 ± 22 mg/dl; ($P < .05$)]. The same pattern was followed for VLDL+LDL cholesterol: lard significantly increased VLDL + LDL cholesterol ($P < .01$) and the corn oil diet significantly decreased it ($P < .01$). The change in HDL was in the opposite direction: lard significantly decreased HDL ($P < .01$) compared to the CNTL diet, and then the corn oil diet significantly increased it compared to the lard diet ($P < .05$).

Zanni et al. (1987) examined the effects of corn oil (31% of calories) and lard (31% of calories) on lipids with and without added cholesterol in healthy women. Each treatment lasted 15 days, followed by 3 weeks of an ad libitum diet. The corn oil treatment significantly decreased ($P < 0.05$) total, LDL and HDL cholesterol compared to the ad libitum diet; however there was no change in the HDL/TC ratio. When compared to the corn oil diet, lard significantly increased ($P < .05$) total cholesterol and HDL cholesterol.

Snook et al. (1985) studied the effects of moderate and very low fat formulas (each for 7 days) compared to a conventional diet, with 42% of energy primarily as butter fat, in 12 college students. The corn oil formula (32% of calories as corn oil, moderate fat diet 1) significantly decreased cholesterol by 25% ($P = 0.05$) and the total cholesterol/HDL cholesterol ratio by 13% even though the HDL level significantly decreased ($P = 0.05$). Furthermore, the corn oil diet (moderate fat diet 1) significantly decreased total cholesterol compared to a low fat diet ($P < 0.05$). Snook et al. (1996) showed that a moderate fat formula diet (32% of calories as corn oil) with a high P/S ratio affected blood lipids more positively than a low fat formula.

Fisher et al. (1983) studied the effects of fat saturation and fat on plasma lipids in 9 healthy males in 4 diet treatments. Corn oil or coconut oil provided 31% of calories. One gram of cholesterol was added to each diet to assess the effects of fat saturation. After a 1-month run-in period (ad libitum), the corn oil diets (31% of calories from corn oil and corn oil + 1 g cholesterol/day) (9 days each) significantly decreased total cholesterol compared to the ad libitum diet (150 ± 18 to 115 ± 12; $P < 0.001$), and the coconut oil diets (31% of calories from coconut oil and coconut oil + 1 g of cholesterol/day) significantly increased it (150 ± 18 to 172 ± 28; $P < 0.05$). (Note: Because there were no differences in blood lipid values between the test oil and the test oil + cholesterol diets, the results were combined for each oil in additional statistical analyses.) The corn oil diets significantly decreased IDL+LDL compared to the ad libitum diet (97 ± 21 to 68 ± 15; $P < 0.001$). The corn oil diets also significantly decreased HDL ($P < 0.01$). The coconut oil diets significantly raised all lipid values compared to corn oil ($P < 0.01$). As mentioned, the hypolipidemic effect of corn oil persisted even with the addition of 1 g of cholesterol a day.

The 3 "Ø" rated Design Type 3 studies found that corn-oil containing diets decreased total cholesterol (Kaplan et al. 1965; Kingsbury et al. 1961; Grande et al. 1958).

Kaplan et al. (1965) examined the effects of corn oil added to skim milk versus a milk and cream diet on lipid levels in 8 peptic ulcer subjects for 2 weeks per treatment. The milk and cream diet (53% fat, 31% SFA) significantly increased ($P < 0.001$) total cholesterol over the corn oil plus skim milk diet (48% fat, 11% SFA). The corn oil plus skim milk diet significantly lowered cholesterol from baseline (226 to 192 mg/dl; $P < .05$), and the milk and cream diet increased it (226 to 245-276 mg/dl; *P value* not reported).

Kingsbury et al. (1961) studied the effects of corn oil versus cod liver oil on plasma cholesterol levels in 11 healthy males with normal, low or elevated blood cholesterol levels for 10-12 days. Both corn oil and cod liver oil decreased total cholesterol by 20-25%. No *P* values were provided.

Using a switch-back study design, Grande et al. (1958) examined differences among oils (corn, olive, cottonseed, sunflower and safflower oils) with and without a dietary supplement of phytosterols in 93 healthy schizophrenic men. One hundred grams of the experimental fat added were added to a low fat diet for a total of 28% calories from fat. The dietary supplements of 0.88 g of unsaponifiable matter from corn oil (the amount found in 55 g of corn oil) were added to a mixture of safflower and cottonseed oil. Based on the Keys et al. (1957) equation, observed versus predicted total cholesterol values were examined. Corn oil resulted in lower serum cholesterol values (by 6.4 to 11.8 mg/100 mL; average 9 mg/100 mL) than those predicted by the Keys multiple regression equation, which is based on fatty acid composition.

The 1 "Ø/-" rated Design Type 3 study (Lloyd et al. 1962) found children with diabetes who were given corn oil at 40% of their caloric needs for at least 6 months (N=16) had significantly lower (P = 0.05) total cholesterol levels (176 $\pm$ 26 mg/100mL) than those in the control group (199 $\pm$ 135 mg/100mL), who received 43% energy from primarily animal fat (N=15). The lower lipid levels in corn oil group were attributed to the high content of PUFAs in the diet.

Three of the 4 "-" rated Design Type 3 studies (Chance et al. 1969; Haust and Beveridge 1964; Horlick 1959) also found reductions in total cholesterol or β lipoprotein cholesterol. The fourth "-" rated Design Type 3 study (Engelberg 1957) found no change in serum cholesterol levels when corn oil was added to the reduced fat diet of patients who had followed this diet for several years,.

Chance et al. (1969), in an early study with 34 children with diabetes who received a corn oil diet or a standard regulated carbohydrate diet, found that mean values for all serum lipids decreased more in the corn oil group than in the control group for the first 5 years of the study. In the 8- to 10-yr-olds, total serum cholesterol was significantly lower (P < .05) in the corn oil group than in the control group. After the first 5 years, the trend was reversed, but obtaining foods prepared with corn oil was difficult.

In a study that examined 2 subjects who were crossed over from a fat free formula for 8 days to a corn oil formula (60% total energy from corn oil) for 8 days (Haust and Beveridge 1963), total cholesterol decreased in both subjects. Fecal cholesterol excretion was 4 to 5 times higher in the corn oil group than in the fat free group.

Horlick (1959) studied 6 healthy subjects by comparing a very low fat diet (4% total energy) versus the same diet with up to 40% of calories (up to 70 g/day) from corn oil for 1 to 2 weeks. Serum cholesterol decreased initially on the low fat diet, with no additional decline on the corn oil diet. The addition of corn oil resulted in a significant drop in β lipoprotein cholesterol from the control diet (P < .0001) and from the low fat diet (P < .0001).

Engelberg (1957) examined a group of private patients (N=12) who had been on a reduced fat diet for several years and showed decreases in serum cholesterol levels in the previous year. The addition of 15-30 g of corn oil for 3 to 9 months did not change total or LDL cholesterol levels further. No statistical analyses were conducted. The reduced fat diet was characterized as being reduced in animal fat, containing 40 to 50 g of fat per day. Six eggs were allowed per week. Milk fat and butter were eliminated from the diet and fat from meat was significantly reduced. No other dietary intake data were provided. Comparisons between the 2 diets and compliance were not measured. Engelberg (1957) concluded that corn oil would be advantageous to add to diets of patients who needed to lower blood lipids.

Subjects with High Blood Cholesterol or Existing CHD

Three studies were conducted: 1 in subjects with hypercholesterolemia and 2 in MI patients. All subjects showed improvement in serum cholesterol levels.

In 2 "Ø" rated Design Type 3 studies, 1 in subjects with hypercholesterolemia (definition not provided) (Rhoads and Barker 1959) and 1 in 28 male MI patients (Watson 1963), serum lipids improved.

Rhoads and Barker (1959) found in 9 hypercholesterolemic subjects that the addition of 90 cc of corn oil to either a low fat or routine hospital diet decreased total cholesterol -32 mg/100 ml (change from a low fat diet to a low fat plus 90 cc corn oil) and -40 mg/100 mL (change from routine hospital diet to a hospital diet + 90 cc corn oil) from baseline, respectively. No statistical analyses were provided. The study periods lasted from 62 to 92 days.

In a long-term, 2- to 3-year study, Watson (1963) found that male MI patients whose diets were supplemented with liquid corn oil (57 g, 2 ounces) (41.5% of fat; 56% linoleic acid content) as part of a 1600- or 2000-calorie low animal fat diet experienced a significant drop in total cholesterol and sustained this level for 3 years ($P < 0.02$). The mean difference from baseline was -41 mg/100 ml ($P < 0.001$). The mean differences from baseline after 1 and 2 years were -72 mg ($P < 0.001$) and -58 mg ($P < 0.001$), respectively. The mean cholesterol level fell 29.1% from months 3-24.

In the 1 "-" rated study, Tobian and Tuna (1958) examined the ability of corn oil to lower cholesterol in 23 coronary atherosclerosis patients who had a history of MI or angina. One to 1.5 ounces of corn oil was consumed before each meal for 12 days and then blood lipids were compared to the pretreatment diet. Eighteen patients were given dietary instructions (avoid butter fat, margarine, hydrogenated oils and consume not more than 1 egg per day) and 5 were not. For the corn oil diet, total cholesterol dropped 9 to 15% and phospholipids dropped from 272 mg/dl to 250 mg/dl. No statistics were provided.

Design Type 4: Cross-Sectional Studies, Analyses of Secondary Disease Endpoints in Intervention Trials and Case Series

In a NA case report, Carlson and Sterner (1960) found that supplementing the diet of 2 children for 10 weeks with 50 g of corn oil resulted in a significant drop in serum cholesterol from 400 mg/100 mL to 260-300 mg/100 mL. Three months after corn oil supplementation was withdrawn, the serum cholesterol results returned to 400 mg/mL.

In another NA case report, Albutt and Chance (1969) found no differences between groups when they compared the fatty acid composition of fasting plasma cholesteryl esters in diabetic children who followed a diet high in corn oil to diabetic children on a standard diabetic diet. The amounts varied widely and were influenced both by the children's age and the amount of linoleic acid in the diet. This report provided no study details; therefore, it was not rated and it is not included in the evidence summary.

Meta-Analyses and Systematic Reviews

No meta-analyses or systematic reviews have been conducted on corn oil. A review by Dupont et al. (1990) concludes that corn oil lowers serum cholesterol due to its low SFA and high PUFA composition and that this combination is more effective in reducing cholesterol than simply decreasing SFA content of the diet.

Animal Studies

Both animal studies showed that corn oil or corn oil fiber improved serum cholesterol levels.

In a "+" rated randomized, controlled study in male Hartley guinea pigs, Ramjiganesh et al. (2002) found that corn fiber oil at 15 g/100 g for 4 weeks lowered total cholesterol -53% ($P < 0.0005$) and LDL cholesterol -57% ($P < 0.0005$). The hyperlipidemic effects of corn fiber oil were not significantly different from the diet containing corn oil at the level of 15 g/100 g. However, the corn fiber oil diet significantly lowered the hepatic cholesterol pool as well as the microsomal cholesterol concentration ($P < 0.010$; $P < 0.0001$). The authors found an up-regulation of the hepatic LDL receptors, which improved processing of LDL particles, resulting in the reduction of LDL cholesterol. A similar effect on the hepatic cholesterol pool was found with corn oil ($P < 0.01$).

In a "-" rated study, Anonymous (1958) examined the effects of oils with varying degrees of saturation on serum cholesterol levels and on incidence of atherosclerosis in forty 8-week-old White Rock cockerels. The birds fed a diet of 10% corn oil had consistently lower cholesterol levels than those fed cottonseed oil with no differences in atherosclerosis. In a second study, the birds fed 17.8% whole corn germ (56% lipid) were significantly protected against early lesions from atherosclerosis.

RELEVANCE ***

The relevance rating deals with the clinical importance of the results (are they physiologically meaningful and achievable) as well as with the generalizability of the results to the target population. The first 4 questions on the Quality Criteria Checklist aid in this assessment: 1) "Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? 2) Did the authors study an outcome (dependent variable or topic) that the patients/clients/population group would care about? 3) Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern…? 4) Is the intervention or procedure feasible?"

The responses to these questions for each study are found in Appendices D-O on the Tally Sheets for each type of study design. More than 95% of the responses to Design Type 1 and Design Type 3 studies are "Yes".

To summarize the responses to relevance questions:

1) Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group?

Yes, the implementation of the intervention, substitution of corn oil containing PUFAs, MUFAs and phytosterols for saturated fat, results in improved outcomes for CHD. In Design Type 1 and Type 3 studies, the relevance to disease reduction is high, with total and LDL cholesterol levels decreasing consistently from 8-25% and 12-29%, respectively, which translates into at least a 16-24% reduction in risk of CHD. This action occurs in both normolipidemic subjects and those with high blood cholesterol levels. Importantly, these studies also demonstrate that middle-aged and elderly subjects with LDL cholesterol levels greater than 130 mg/dl, when placed on a National Cholesterol Education Program Step 2 diet, can achieve significant reductions in LDL cholesterol. These reductions in LDL cholesterol occur by including vegetable oils high in PUFAs, such as corn oil, and decreasing the amount of saturated fat and cholesterol. These LDL reductions translate to significant reductions in CHD. A 1% reduction in LDL cholesterol translates to a 2% reduction in risk for CHD (Kris-Etherton et al. 2004; NCEP 2002). Kris-Etherton et al. (2004) reviewed studies (summarized in their table 2) that used diets with 8-9% of energy from saturated fat and 14-21% calories from PUFAs. They concluded that such diets reduce LDL cholesterol levels by 13-15%, which was associated with a 25-43% decrease in CHD events.

2) Did the authors study an outcome (dependent variable or topic) that the patients/clients/population group would care about?

People are concerned about CHD. A recent US study (N=1001) found that 42% of shoppers have purchased a product based on the CHD health claim, reduced risk of heart disease (FMI, *Prevention and Rodale Inc.* 2004). Furthermore, shoppers indicate that they or someone in their household has (37%) or is at risk for (12%) high cholesterol.

3) Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern ...?

Yes, CVD is a common issue of concern. CVD has been the primary cause of death in the United States (except for 1918) (AHA 2005, 2006). CHD is considered a type of CVD (AHA 2005, 2006) and in 2003 was the underlying or contributing cause of 58% of deaths (AHA 2006). CHD direct and indirect costs are estimated to be $142.5 billion in 2006, and CVD direct and indirect costs are estimated to exceed $430 billion (AHA 2006). Dietary and lifestyle changes can contribute to a reduced risk of CHD.

4) Is the intervention or procedure feasible?"

The intervention, substituting corn oil for saturated fat, is feasible. Studies using corn oil have been conducted for as long as 3 years (Grande et al. 1958). The US population has been using corn oil in their diets since the early 1900s. Current per capita consumption of corn oil is 6.2 pounds per year or 7.05% of fat consumption (USDA ERS 2004).

EVIDENCE SUMMARY: MECHANISM OF ACTION AND OTHER EFFECTS

EFFECT OF PHYTOSTEROLS DESIGN TYPE 1, DESIGN TYPE 3 AND ANALYTICAL STUDIES

Seven studies were reviewed (see Appendix I Evidence Table and Tally Sheet) to determine the effect of phytosterols on blood lipids or cholesterol absorption.

Three "+" rated Design Type 1 studies conducted on 51 healthy people examined the potential mechanisms for the lipid lowering effects of corn oil [Ostlund et al. 2002 (N=20); Howell et al. 1998 (N=16); Kohlmeier et al. 1988 (N=15)]. All are of "+" quality. **Two Design Type 3** studies were conducted on 95 subjects [Haust and Beveridge 1963 (N=2); Grande et al. 1958 (N=93)]. One study was rated "Ø" (Grande et al. 1958); 1 was rated "-" (Haust and Beveridge 1963). Two laboratory analyses were rated NA (Moreau et al. 1999; Milkova et al. 1977).

All 3 rated "+" Design Type 1 studies concluded that phytosterols most likely contributed to the ability of corn oil to positively affect blood cholesterol levels.

Ostlund et al. (2002) found that both phytosterols naturally present in corn oil (not removed through special processing) and corn oil phytosterols that were added back to purified corn oil significantly reduced cholesterol absorption, -27.5% $\pm$ 7.4% (P < 0.01) and -27.9% $\pm$ 9.1%(P = 0.01), respectively. (Note: For this study only, purified corn oil has the phytosterols removed. The corn oil consumed by the public, whether purified, refined, bleached and/or deodorized, still contains phytosterols.) This reduced cholesterol absorption probably contributes to the ability of corn oil to lower blood cholesterol levels.

Using a randomized Latin-square design, Howell et al. (1998) examined the effect of 3 treatments–phytosterols present in corn oil, olive oil and olive oil enriched with phytosterols–on plasma lipids in 16 normolipidemic subjects. Each treatment lasted 10 days, separated by a washout period of 2 weeks of an ad libitum diet prior to the next treatment. All meals were prepared and consumed in a metabolic unit. The corn oil diet and the enriched olive oil diet contained 830 mg phytosterols/100 g of oil. Both olive oil diets resulted in significantly higher total cholesterol levels (P = 0.001) than did the corn oil diet, and the olive oil diet resulted in significantly higher LDL cholesterol (P < .05). When phytosterols were added to olive oil (enriched olive oil diet), there was no difference in LDL cholesterol between this diet and the corn oil diet Therefore, the authors concluded that the phytosterols naturally present in corn oil contributed to the differences among the treatments.

In a randomized, crossover trial with 4-week treatment and 6-week washout periods, Kohlmeier et al. (1988) found that 75 g of corn oil products significantly lowered total cholesterol (-25%) ($P \leq$ 0.001) and LDL cholesterol (-29.3%) ($P \leq$ 0.001) in 15 healthy men with higher than average cholesterol levels (5.2-6.7 mmol/L). This lipid lowering effect was significantly greater than with sunflower oil (P < .01). HDL levels were not changed. These subjects also had a significantly higher sterol excretion on the corn oil diet compared to that on an unrestricted normal diet ($P \leq$ .05). Furthermore, Kohlmeier et al. (1988) demonstrated a strong inverse correlation between the change in serum cholesterol levels and the change in endogenous sterol excretion. The corn oil diet contained 35 g corn oil and 40 g of corn oil margarine.

In the "-" rated early study, Haust and Beveridge (1963) examined 2 subjects who were crossed over from a fat free formula for 8 days to a corn oil formula (60% total energy from corn oil) for 8 days. Total cholesterol decreased in both subjects. Fecal cholesterol excretion was 4 to 5 times higher in the corn oil group than in the fat free group.

Using a switch-back study design, Grande et al. (1958) examined differences among oils (corn, olive, cottonseed, sunflower and safflower oils) with and without a dietary supplement of phytosterols in 93 healthy, schizophrenic men. One hundred grams of the experimental fat added were added to a low fat diet for a total of 28% calories from fat. The dietary supplements of 0.88 g of unsaponifiable matter from corn oil (the amount found in 55 g of corn oil) were added to a mixture of safflower and cottonseed oil. Based on the Keys equation (Keys et al. 1957), observed versus predicted total cholesterol values were examined. Corn oil resulted in lower serum cholesterol values (by 6.4 to 11.8 mg/100 mL; average 9 mg/100 mL) than those predicted by the Keys et al. (1957) multiple regression equation, which is based on fatty acid composition. The addition of the dietary supplement of unsaponifiable matter to the other oil treatments resulted in a small difference of 3.2 mg% compared with the oil treatments alone. The authors concluded that the unsaponifiable matter found in 100 g of corn oil lowers serum cholesterol an additional 6 to 12 mg/100 mL.

EFFECTS ON ATHEROGENICITY/OXIDATIVE MODIFICATION OF LDL DESIGN TYPE 1 AND DESIGN TYPE 3 STUDIES

Three studies examined atherogenicity/oxidative modification of LDL in persons with LDL cholesterol > 130 mg/dl (Cuchel et al. 1996 (N=14); Schwab et al. 2000 (N=13); Schwab et al. 1998 (N=14) (see Appendix J Evidence Table and Tally Sheet). **The Design Type 3** study is of "+" quality (Cuchel et al. 1996) and **both Design Type 1** studies are of "0" quality (Schwab et al. 2000; Schwab et al. 1998).

Scientists have postulated that the oxidative modification of LDL may increase its atherogenicity. Three studies (Schwab et al. 2000; Schwab et al. 1998; Cuchel et al. 1996) on a similar group of middle-aged and elderly moderately hypercholesterolemic subjects found no difference in LDL susceptibility to oxidation on reduced fat diets with various fats and forms of fats. Schwab et al. (2000) examined 13 hypercholesterolemic subjects and found dietary cholesterol added to reduced fat diets high in PUFA or SFA increased LDL susceptibility to oxidation. Schwab et al. (1998) found no differences in the in vitro susceptibility of LDL to oxidation in those subjects consuming reduced-fat diets (30% kcal from fat) enriched with animal or vegetable oils. The dietary interventions included a wide range of fatty acid profiles: corn oil, canola, olive oil, rice bran oil and beef tallow. Cuchel et al. (1996) found replacing corn oil with corn oil margarine in sticks did not affect LDL susceptibility to oxidation.

POSTPRANDIAL EFFECTS ON BLOOD LIPIDS DESIGN TYPE 1 AND DESIGN TYPE 3 STUDIES

Four studies examined the effect of corn oil on postprandial blood lipids (see Appendix K Evidence Table and Tally Sheet).

Three Design Type 1 RCTs have been conducted with 35 healthy people [Muesing et al. 1995 (N=12); Zampelas et al. 1994 (N=11); Schlierf et al. 1979 (N=12).] Two are of "+" quality (Muesing et al. 1995; Zampelas et al. 1994) and 1 is of "-" quality (Schlierf et al. 1979). **One Design Type 3** study of "-" quality was conducted [Tall et al. 1982 (N=6)].

Postprandial lipemia persists for several hours after a meal. Muesing et al. (1995) hypothesized this postprandial lipemia may be more predictive of CHD than fasting levels of blood lipids. HDL may be of special interest. HDL levels have a strong inverse correlation with CHD because HDL transports cholesterol out of the cells. When comparing corn oil and beef tallow, Muesing et al. (1995) found no difference between corn oil and beef tallow in HDL increases postprandially (7-10 hours). However, LDL-C was significantly higher (P = 0.003) with beef tallow than with corn oil; and triglyceride responses were significantly higher with corn oil. These differences suggest that fat metabolic mechanisms differ based upon the type of fat consumed.

Zampelas et al. (1994) found that there were no differences between *n*-6 and *n*-3 fatty acids on postprandial plasma-triglyceride responses, and none in any measure of postprandial lipids and apolipoprotein levels in 12 healthy men. Schlierf et al. (1979) found in healthy young males a diurnal increase of lecithin-cholesterol acyl transferase activity on a corn oil diet but not on a palm oil diet. The palm oil diet resulted in a significant correlation between postprandial hepatic lipase and postprandial plasma triglycerides.

In the "-" rated study, Tall et al. (1982), when evaluating the effects of 2 different corn oil meals, consumed by 6 subjects, found that 100 mL of corn oil increased triglycerides significantly more ($P < 0.01$) than 80 mL of corn oil plus 4 eggs. Both meals increased the lipoprotein mass in both HDL peaks and both resulted in a redistribution of HDL into lower density subclasses. This redistribution of HDL did not alter the size or composition of HDL particles in individual subclasses.

EVIDENCE SUMMARY: PUFAs AND CHD/CVD

Several trials conducted in the 1950s and 1960s were the foundation for the conclusions that vegetable oils high in PUFAs reduce serum cholesterol levels, thereby decreasing the risk for CHD. When vegetable oils high in PUFAs replaced saturated fat in the diet, blood cholesterol lipoprotein cholesterol levels were significantly decreased (Keys et al. 1957). The results of these early studies provided the foundation for equations that predicted blood cholesterol lowering responses by PUFAs.

DESIGN TYPE 1: RANDOMIZED, CONTROLLED, INTERVENTION TRIALS

The Macronutrient Report (IOM 2002/2005) concluded that *n*-6 PUFAs decrease LDL cholesterol compared to saturated fat. Furthermore, higher *n*-6 PUFA intakes generally improve blood lipid profiles, which results in a decreased risk for CHD. Six intervention studies provided in Table 11-9 of the Macronutrient Report illustrate that higher intakes of *n*-6 PUFAs improve lipid profiles [Howard et al. 1995 (N=63); Zock and Katan 1992 (N=56); McDonald et al. 1989 (N=8); Mattson and Grundy 1985 (N=20); Kris-Etherton et al. 1993 (N=30-33); Becker et al. 1983 (N=12)] (see Appendix L Evidence Table and Tally Sheet).

Three studies are rated as "+" (Howard et al. 1995; Kris-Etherton et al. 1993; Zock and Katan 1992) and 3 are rated as "Ø" (McDonald et al. 1989; Mattson and Grundy 1985; Becker et al. 1983). The *2005 Dietary Guidelines for Americans* Advisory Committee Report (2005 DGAC 2004) also supports this conclusion and references the Macronutrient Report.

DESIGN TYPE 2: PROSPECTIVE, OBSERVATIONAL, COHORT STUDIES; DESIGN TYPE 3: NONRANDOMIZED, INTERVENTION TRIALS WITH CONCURRENT OR HISTORICAL CONTROLS AND CASE-CONTROL STUDIES; AND DESIGN TYPE 4 STUDIES

The *2005 Dietary Guidelines for Americans* Advisory Committee Report (2005 DGAC 2004) evaluated the epidemiologic studies that have examined the association between *n*-6 PUFAs and CVD (Kark et al. 2003; Hegsted and Ausman 1988; Hu et al. 1997; Keys 1997; Ascherio et al. 1996; Kromhout et al. 1995; Tell et al. 1994; Artaud-Wild et al. 1993; Posner et al. 1991; Joossens et al. 1989; Kushi et al. 1985; Shekelle et al. 1981; Gordon et al. 1981; Garcia-Palmieri et al. 1980).

A positive association was found between the intake of PUFAs and a reduced risk of CVD morbidity and mortality (Hu et al. 1997; Ascherio et al. 1996; Tell et al. 1994; Artaud-Wild et al. 1993; Hegsted and Ausman 1988; Joossens et al. 1989; Shekelle et al. 1981; Gordon et al. 1981; Garcia-Palmieri et al. 1980). A few other studies found no association or no beneficial association between PUFAs and CVD (Keys 1997; Kromhout et al. 1995; Kark et al. 2003; Kushi et al. 1985; Posner et al. 1991). A recently published study (Laaksonen et al. 2005) found an inverse association between those with a linoleic acid intake in the upper third and those with dietary PUFA in the upper third and a reduced risk of CVD mortality, -61% and -62%, respectively.

Of the above studies, **7 were Design Type 2**, conducted with 151,729 healthy people [Laaksonen et al. 2005 (N=1551); Keys et al. 1997 (N=12,763); Hu et al. 1997 (N=80,082); Ascherio et al. 1996 (N=43,757); Kromhout et al. 1995 (N=12,763); Posner et al. 1991 (2 male cohorts: N=420 and 393); Shekelle et al. 1981 (N=1900)] (see Appendix M Evidence Table and Tally Sheet). Four studies are rated "+" (Laaksonen et al. 2005; Keys et al. 1997; Hu et al 1997; Ascherio et al. 1996); 1 is rated "Ø/+" (Shekelle et al. 1981); and 2 are rated "Ø" (Kromhout et al. 1995; Posner et al. 1991).

Of the above studies, **9 were Design Type 3**, conducted with large samples [Kark et al. 2003 (N=672); Tell et al. 1994 (N=13,148); Artaud-Wild 1993 (N=40 countries); Joossens et al. 1989 (N=5,264,948); Hegsted and Ausman 1988 (N=18 countries); Kushi et al.1985 (N=1001); Gordon et al. 1981(N=16,349); Garcia-Palmieri et al. 1980 (N=8218); Keys et al. 1957 (N=84)] (see Appendix N Evidence Table and Tally Sheet). Seven studies are rated "+" [Kark et al. 2003; Tell et al. 1994; Artaud-Wild 1993; Kushi et al. 1985; Gordon et al. 1981; Garcia-Palmieri et al. 1980; Keys et al. 1957); 1 is rated "Ø" (Joossens et al. 1989); and 1 is rated "-" (Hegsted and Ausman 1988).

The Advisory Committee Report included 1 "+" rated **Design Type 4** study [Djoussé et al. 2001 (N=4594)] (see Appendix O Evidence Table and Tally Sheet).

REVIEWS

One systematic review [Hu and Willett 2002 (N=147 studies)] and 4 other reviews [Kris-Etherton et al. 2004; Sacks and Katan 2002 (11 trials, 4 PUFA); Hu et al. 2001; Mock 1959] establish that substituting *n*-6 PUFAs for saturated fat is related to a reduced risk of CHD. Three studies are rated "Ø" and 2 are classified as "NA" because there is insufficient information on methodology of the review (Kris-Etherton et al. 2004; Mock 1959) and because there is no summary of the results (Mock 1959). The latter citation resulted from the PubMed searches for corn oil.

ANIMAL STUDIES

Nonhuman primate studies conducted by Rudel and his group clearly demonstrate that *n*-6 PUFAs protect against and decrease coronary atherosclerosis. According to Rudel et al. (1995a), MUFAs have not demonstrated the same effect. Importantly, this effect, *n*-6 PUFAs protection against and decrease of coronary atherosclerosis, was demonstrated in juvenile African green monkeys, which has positive implications for childhood diets containing *n*-6 PUFAs (Wolfe et al. 1994). Four Design Type 3 studies were examined in African green monkeys (less susceptible to diet-induced atherosclerosis) and cynomolgus monkeys (easily susceptible to diet-induced atherosclerosis) [Rudel et al. 1997 (N=44); Rudel et al. 1995a (N=44); Rudel et al. 1995b (N=74); Wolfe et al. 1994 (N=108)]. All are rated as "+."

Rudel et al. (1995a) tested the substitution of a high PUFA diet (>70% linoleic acid) or a high MUFA diet (>70% oleic acid) for 1 high in saturated fat (40% palmitic acid) on the degree of coronary atherosclerosis in African green monkeys. These monkeys are similar to humans in their responsiveness to dietary fat and the effects of plasma lipoproteins and in their atherosclerotic lesions. Coronary atherosclerosis, determined by intimal area, was significantly less ($P = 0.05$) in the high PUFA diet versus the saturated fat and high MUFA diets. This positive result occurred even though there were no differences between the PUFA and MUFA diets in LDL cholesterol. Furthermore, HDL significantly increased on the high MUFA diet versus the high PUFA diet (P = 0.0001). Luminal stenosis was significantly different between the PUFA and the SFA diets (P < 0.05).The authors concluded a high PUFA diet results in the least amount of atherosclerosis because it prevents the accumulation of cholesteryl oleate in LDL and in coronary arteries.

In another study that compared the response of African green monkeys to cynomolgus monkeys, Rudel et al. (1995b) examined the effects of PUFA and SFA diets with and without cholesterol (low and high). The treatment periods ranged from 3 years for the cynomolgus monkeys to 5 years for the African green monkeys. The latter take longer to develop atherosclerosis. When the high PUFA diet (linoleic acid; 28% TE from PUFA) and a high SFA diet (16% TE from SFA) were compared, the high cholesterol high PUFA diet significantly decreased (P < 0.01) atherosclerosis in contrast to the high cholesterol high SFA diet. The coronary artery atherosclerosis was highly related to LDL cholesteryl oleate (r = 0.8, P < 0.001). Coronary artery atherosclerosis also was highly correlated with mean LDL for all groups (r = 0.9, P < 0.0001). Total cholesterol was significantly decreased in both species when a PUFA versus an SFA diet was fed ($P \leq 0.05$). LDL tended to be 20% lower when a PUFA diet was compared to an SFA diet, but the difference was not statistically significant.

Rudel et al. (1997) further studied the correlation among diet (35% calories as fat as PUFA, MUFA or SFA), plasma cholesterol, cholesterol secretion by the perfused liver and coronary artery atherosclerosis in 44 adult African green monkeys. After an 8-week challenge diet, the monkeys were placed on a PUFA diet (greater than 70% linoleic acid), a MUFA diet (greater than 70% oleic acid) or an SFA diet (greater than 40% palmitic acid) for 5 years. The MUFA diet resulted in livers with higher cholesteryl ester concentrations than the livers for the other groups. Cholesteryl oleate was higher in the MUFA group versus the SFA group. In both the MUFA and SFA groups, the liver perfusate cholesteryl ester accumulation rate was highly correlated ($r \geq 0.8$) with coronary artery cholesteryl ester concentration. The latter is an indicator of the degree of coronary artery atherosclerosis. The authors concluded that the significant amount of cholesteryl oleate enrichment in MUFA plasma cholesteryl esters may cause the high amount of coronary artery atherosclerosis in the MUFA group.

In a study conducted with 108 juvenile African green monkeys, Wolfe et al. (1994) evaluated the effects of a PUFA or an SFA diet (diets providing 40% calories from fat) on coronary atherosclerosis. The study was conducted from birth until death at 16, 32 or 60 months. The mothers consumed the same diets before and during pregnancy. The PUFA group had significantly less maximal intimal thickness (P = 0.007) and significantly smaller lesions (P = 0.007) than the SFA group. This occurred despite a significant decrease (P =0.0005) in HDL in the PUFA versus the SFA groups. These results suggest that intervention with n-6 PUFAs early in life decreases the amount of coronary atherosclerosis later in life.

REQUIRED SCIENTIFIC SUMMARY ISSUES TO BE ADDRESSED

IS THERE AN OPTIMUM LEVEL OF THE PARTICULAR SUBSTANCE TO BE CONSUMED BEYOND WHICH NO BENEFIT WOULD BE EXPECTED?

The optimum level for n-6 PUFAs is 8 to 10% of calories. Current mean consumption levels of n-6 PUFAs are 5 to 6% of total caloric intake (Allison et al. 1999; CSFIII 1989-91 data). Intakes for children and adolescents vary depending on age and ethnic group, but range from 6 to 8% (Troiano et al. 2000).

The IOM Report (2002/2005) set an Adequate Intake (AI) for linoleic acid, the predominant *n*-6 PUFA, at 5% of calories. The Acceptable Macronutrient Distribution Range (AMDR) for linoleic acid has been set at 5 to 10% of energy.

Of those Design Type 1 studies of at least 21 days duration, corn oil intake ranged between 20% (44 g/2000 kcal) (Lichtenstein et al. 1993b) and 34% of calories (75.5 g/2000 kcal) (Wardlaw and Snook 1990), resulting in a drop of -13.6% and -14% in total cholesterol and -17.8% and -13% in LDL cholesterol, respectively, versus the baseline diets (see Appendices D3 and R). Therefore, it appears the lower amount of 20% of calories (44 g /2000 kcal) from corn oil is just as effective as the higher amount of 34% of calories (75.5 g/2000 kcal). When compared to beef tallow, a corn oil intake of 20% of calories resulted in an approximately 11% greater drop in total cholesterol and a 9% greater drop LDL cholesterol (Lichtenstein et al. 1994a). When compared to butter, a corn oil intake of 34% of calories resulted in a difference of -21% in total cholesterol and -26% in LDL cholesterol.

MINIMUM EFFECTIVE AMOUNT OF CORN OIL IN FOODS ELIGIBLE FOR THE HEALTH CLAIM

According to the Code of Federal Regulation's general requirements for health claims, if the claim is about the effects of consuming the substance at other than decreased dietary levels, the level of the substance must be sufficiently high and in the appropriate form to justify the claim. Where no definition of "high" has been established, the claim must specify the daily dietary intake necessary to achieve the health claim's effect [21 CFR101.14(d)(2)(vii)].

The proposed DV (minimum effective amount) would be 11.2 g of corn oil (6.6 g of PUFAs) (see Appendix R). This DV is based on CFSAN calculations for the Monounsaturated Fatty Acids from Olive Oil health claim (FDA 2004). The minimum effective amount of corn oil (as indicated by PUFA content) necessary as a substitute for saturated fat is determined by calculating the difference in the amount of PUFAs in grams, between the high PUFAs from corn oil and high SFA diets. Therefore, the differences in PUFAs in the high corn oil versus the high saturated fat diets in the "+" Design Type 1 Studies longer than 21 days that provide fatty acid composition of the diet were used (see Appendix R). These studies included Lichtenstein et al. (1994b) (19.10 g vs. beef tallow); Lichtenstein et al. (1993b) (7.26 g vs. baseline diet); Insull et al. (1994) (6.6 g vs. ad libitum); Ng et al. 1991 (23.33 g vs. coconut oil); Wardlaw and Snook 1990 (31.11 g vs. butter; 28.99 g vs. MUFAs); Kohlmeier et al. (1988) (1.6 g vs. sunflower oil); Laine et al. (1982) (40.71 g vs. palm oil; 20 days); Dayton et al. (1969) (25 g of linoleic acid).

The lowest amount of PUFAs from corn oil needed to replace saturated fat that may result in significant reductions in serum total and LDL-cholesterol is 6.6 g (Insull et al. 1994). [The Kohlmeier et al. (1988) value of 1.6 g was not used because it did not reflect the entire diet.] Corn oil contains approximately 59% PUFAs (Dupont 1990). Consuming 11.2 g of corn oil provides approximately 6.6 g PUFAs. Therefore the DV (minimum effective amount) for corn oil would be 11.2 g (6.6 g PUFAs)/day. For the Monounsaturated Fatty Acids from Olive Oil health claim (FDA 2004), FDA determined that the minimum effective dose would be based on 4 eating occasions per day. For corn oil, this would result in 2.8 g of corn oil (1.65 g of PUFAs) to qualify for the health claim.
[Note: Eleven and twenty hundredths grams of corn oil is approximately .80 tablespoon. The RACC for corn oil is 1 tablespoon (14 g), which contains 7.77 g PUFAs.]

IS THERE ANY LEVEL AT WHICH AN ADVERSE EFFECT FROM THE SUBSTANCE OR FROM FOODS CONTAINING THE SUBSTANCE OCCURS FOR ANY SEGMENT OF THE POPULATION?

According to the *2005 Dietary Guidelines* Advisory Committee (2005 DGAC 2004), which conducted a systematic review of the research, no studies reported adverse effects, even with PUFAs at 12% of calories. The Acceptable Macronutrient Distribution Range (AMDR) set by the Institute of Medicine takes into account that evidence for intakes greater than 10% of calories is lacking. The AMDR for linoleic acid is set at 5 to 10% of energy.

In a recent nested case-control study as part of the Japan Collaborative Cohort Study (N= 169 colorectal cancer cases and 481 controls), Kojima et al. (2005) found no negative relationship between high serum levels of *n*-6 PUFAs and colorectal cancer risk.

Several studies included in the evidence-based analysis used higher amounts of corn oil with no or minimal adverse effects [Wagner et al. 2001 (80 g corn oil); Schwab et al. 2000; Schwab et al. 1998; Jones et al. 1994; Lichtenstein et al. 1994a; Lichtenstein et al. 1993a; Lichtenstein et al. 1993b; Laine et al. 1982 (all 20% kcal as corn oil); Lichtenstein et al. 1994b (19% kcal as corn oil); Howell et al. 1998 (23% kcal as corn oil); Ng et al. 1991 (24% kcal as corn coil); Wardlaw and Snook 1990 (34% kcal as corn oil); Kohlmeier et al. 1988 (35 g corn oil, 40 g corn-oil margarine); Childs et al. 1981 (30.5 g corn oil); Dayton et al. 1969 (27% kcal as corn oil); Rose et al. 1965 (50-80 g corn oil)].

WHAT NUTRITIONAL OR HEALTH FACTORS (BOTH POSITIVE AND NEGATIVE) ARE IMPORTANT TO CONSIDER WHEN CONSUMING THE SUBSTANCE?

POSITIVE NUTRITIONAL AND HEALTH FACTORS

The principal constituents of corn oil are acylglycerols, primarily in the form of triglycerides. Corn oil is 59% PUFA (linoleic acid), 24% MUFA and 13% SFA (Dupont et al. 1990). Corn oil favorably affects the nutritional profile of the diet. When corn oil is substituted for butter, saturated fat and cholesterol are decreased, and PUFAs, MUFAs, vitamin E and phytosterols are increased (see Table 2).

Refined corn oil contains about 1.2% of unsaponifiable materials, which include sterols, tocopherols, hydrocarbons and ubiquinone Q9. Corn oil is higher in sterols than all other vegetable oils (Dupont et al. 1990) (see Table 3).

Moreau et al. (1999) examined the effect of heat pretreatment of corn fiber on vitamin E and phytosterol composition. Heat treatment (100-175 °C) resulted in a small decrease in phytosterol components and a large increase in gamma-tocopherol: from 5.4 mg/100 g corn fiber to 52.1 mg of gamma-tocopherol/100 g corn fiber.

Milkova et al. (1977) examined the types of individual sterols present in corn oil using various methods. Sitosterol, campesterol and stigmasterol were found as primary components of all sterol fractions of corn oil and its products. Dehydrocampesterol and other sterols are found as free sterols in raw corn oil.

TABLE 2. NUTRIENT COMPARISON OF CORN OIL AND BUTTER

NUTRIENT	CORN OIL* 14 G	CORN OIL 11.2 G	BUTTER* 14 G	BUTTER 11.2 G
Calories	124	99	100	80
Calories from Fat	124	99	100	80
Fat	14.00 g	11.20	11.36 g	9.08 g
Saturated Fat	1.813 g	1.450 mg	7.192 g	5.753 g
PUFA	7.655 g	6.124 g	0.426 g	0.341 g
MUFA	3.861 g	3.089 g	2.943 g	2.354 g
Trans Fat	0.040 g	0.032 g	-	-
Cholesterol	0 mg	0 mg	30 mg	24 mg
Sodium	0 mg	0 mg	81 mg	65 mg
Total Carbohydrate	0.00 g	0.00 g	0.01 g	0.01g
Dietary Fiber	0.0 g	0.0 g	0.0 g	0.0 g
Sugars	0 g	0.00 g	0 .01g	0.01 g
Protein	0 g	0.00 g	0.12 g	0.10 g
Vitamin A	0 IU	0 IU	350 IU	280 IU
Vitamin C	0 mg	0 mg	0.0 mg	0.0 mg
Calcium	0 mg	0 mg	3 mg	3 mg
Iron	0.00 mg	0 mg	0.00 mg	0.00 mg
Vitamin E	2 IU (2.00 mg alpha-tocopherol)	1.60 IU (1.60 mg alpha-tocopherol)	0.32 IU (0.32 mg alpha-tocopherol)	0.26 IU (0.26 mg alpha-tocopherol)
Phytosterols	136 mg	108 mg	1 mg	0 mg

* USDA 2004 (see Appendix S)

TABLE 3. PHYTOSTEROL CONTENT OF VEGETABLE OILS

VEGETABLE OIL	PHYTOSTEROL CONTENT MG/100G*
Corn oil	968
Canola oil	658**
Safflower oil, > 70% linoleic	444
Safflower oil, > 70% oleic	444
Cottonseed oil	324
Soybean oil	250
Olive oil	221
Peanut oil	207
Sunflower oil, > 60% linoleic	100
Sunflower oil, < 60% linoleic	100
Coconut oil	86
Palm kernel oil	95

* USDA 2004 (see Appendix S)

** (Phillips et al. 2002)

NEGATIVE NUTRITIONAL AND HEALTH FACTORS

When substituted for saturated fat in the diet, corn oil has no inherently negative nutritional factors. When added to the diet corn oil contributes 9 calories per gram.

EFFECT OF THE USE OF THE PROPOSED HEALTH CLAIM ON FOOD CONSUMPTION

The proposed health claim is expected to increase consumer purchases of corn oil. New health claims approved by the FDA usually result in increased sales of the labeled product. However, this product should be substituted for products containing saturated and/or *trans* fat and, therefore, should not result in an increased amount of fat or calories in the diet.

The increased sales of corn oil are expected to affect the composition of the US diet favorably because of the total nutrient profile that corn oil delivers. Corn oil adds PUFAs, such as linoleic acid, and vitamin E and phytosterols. Substitution of 11.2 g of corn oil for 11.2 g of butter results in an increase of +5.78 g of PUFAs, +.74 g of MUFAs, +1.34 IU vitamin E (4.45 % DV) and +108 mg of phytosterols, as well as a decrease of -4.30 g (-21.5 % DV) of saturated fat, -24 mg cholesterol (-8 % DV), -65 mg sodium (-2.7 % DV) and vitamin A -280 IU (-5.6%).

SIGNIFICANT SCIENTIFIC AGREEMENT REQUIREMENTS

The FDA's "Guidance for Industry, Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements" FDA 1999) addresses the components of the scientific review of health claims. The standard of scientific validity states: 1) the totality of the publicly available evidence supports the substance/disease relationship that is the subject of the claim, and 2) there is SSA among qualified experts that the relationship is valid. The scientific review includes 1) identifying the data for review with RCT as the gold standard, 2) assessing appropriate measurement of both the substance and the disease or health-related condition, 3) evaluating individual studies and 4) evaluating the totality of the evidence. The systematic evidence-based analysis includes all of these components.

Under "evaluating the totality of the evidence," FDA (1999) has stated it evaluates the criteria necessary for the determination of a causal relationship between a dietary factor/substance and the reduced risk of a disease or health-related condition. These criteria are addressed below, by summarizing the scientific support. The results of the evidence-based analysis strongly support a causal relationship between the consumption of corn oil and a reduced risk of CHD.

STRENGTH OF THE ASSOCIATION

The evidence-based analysis rates the strength of the total body of evidence by assessing the quantity and type of studies, the consistency of the association of corn oil reducing the total and LDL cholesterol and the relevance of this association to CHD reduction. The strength of the body of evidence is rated as a "B" level health claim (see pp. 16-30).

CONSISTENCY OF THE ASSOCIATION

The evidence-based analyses resulted in a consistency rating of ***. The data from all but 1 of the "+" and "Ø" rated Design Type 1 Randomized, controlled, intervention trials that examined the effect of corn oil on blood lipids with healthy subjects and those with high blood cholesterol levels or existing CHD consistently show that when corn oil replaces saturated fat or other oils or when corn oil is included in the diet, blood lipids are affected favorably. Total and/or LDL cholesterol decreases. All but 1 "+" and "Ø" Design Type 3 studies in normolipidemic and subjects with high blood cholesterol levels show significant reductions in total and/or LDL cholesterol when subjects consumed diets containing corn oil that replaced saturated fat or other oils (see pp. 20-29).

INDEPENDENCE OF THE ASSOCIATION

The independence of the association between corn oil containing PUFAs and the reduction of total and LDL cholesterol is demonstrated through Design Type 1 RCTs, which support that this substance reduces total and/or LDL cholesterol, thereby reducing the risk of CHD (see pp. 19-24). The independence of the association is also demonstrated in these Design Type 1 RCTs when potentially confounding factors are controlled for in the multivariate analyses (see pp. 20-25). Both Design Types 1 and 3 studies strongly support the effects of corn oil reducing the risk of CHD.

DOSE-RESPONSE RELATIONSHIP

There have been no dose-response studies with corn oil containing PUFAs on total and LDL cholesterol. However, the studies conducted use a range in amounts of corn oil that may be related to an effect on total and LDL cholesterol. When compared to beef tallow, a corn oil intake of 20% of calories resulted in an approximately 11% greater drop in total cholesterol and a 9% greater drop LDL cholesterol (Lichtenstein et al. 1994b). When compared to butter, a corn oil intake of 34% of calories resulted in a difference of -21% in total cholesterol and -26% in LDL cholesterol (see Appendix D 3, Table: Corn Oil Design Type I Studies: Postintervention Blood Lipid Concentrations and Appendix R).

TEMPORAL RELATIONSHIP

The clearest evidence for a temporal relationship, i.e., the exposure consistently precedes the outcome, between increased intake of corn oil and a reduced risk of CHD is provided by both the Design Type 1 Randomized, controlled, intervention trials and Design Type 3 Nonrandomized, intervention trials with concurrent or historical controls, where a diet containing corn oil consistently reduces total and/or LDL cholesterol when compared to baseline levels, a control group or another fat treatment (see pp. 20-28).

EFFECT OF DECHALLENGE

Two studies have prospectively examined the effects of a controlled and supervised withdrawal of corn oil containing PUFAs on the subsequent levels of total cholesterol. Watson (1963), as part of a long-term, 2- to 3-year study, found that when 2 ounces of corn oil/day were withdrawn for 5 months, the mean cholesterol level went from 259 mg/dl to 308 mg/dl. The increase reached significance after corn oil was removed for 1 month (rising to 293 mg/dL) ($P < .05$). Once the corn oil was restarted, the mean levels dropped back to 280 mg/dl after 2 months. This group of subjects, prior to this experiment, had been on the corn oil diet for 1 year and had experienced a significant drop in total cholesterol from baseline. Dayton et al. (1969) found a similar effect within 2 weeks of the cessation of their study.

An earlier case study has suggested that the effects of corn oil can "wear off." Carlson and Sterner (1960) found that supplementing the diet of 2 children for 10 weeks with 50 g of corn oil resulted in a significant drop in serum cholesterol from 400 mg/dl to 260-300 mg. Three months after corn oil supplementation was withdrawn, the serum cholesterol rebounded to 400 mg/dl. The withdrawal of corn oil was associated with a loss of the beneficial effects.

SPECIFICITY

Specificity means the degree to which the substance is associated with only the disease in question. The Design Type 1 RCTs discussed in this evidence analysis demonstrate that corn oil reduces total and/or LDL cholesterol, thereby reducing the risk of CHD.

BIOLOGICAL PLAUSIBILITY

Currently, the most plausible mechanism to explain the reduction in risk for CHD with increased corn oil is through its effect on reduction of total and LDL cholesterol. This lipid lowering effect is demonstrated by all but 1 Design Type 1 RCTs studies and all but 1 Design Type 3 studies. Additionally, the phytosterols naturally present in corn oil decrease the absorption of cholesterol as demonstrated by 3 "+" rated (Ostlund et al. 2002; Kohlmeier et al. 1988; Howell et al. 1998) and 2 "-" rated Design Type 1 studies (Haust and Beveridge 1963; Grande et al. 1958).

OVERALL CONCLUSION

The information presented in this proposed health claim petition for corn oil and CHD fulfills the requirements for a "B" level health claim. First, the results of the evidence-based ranking system demonstrate that the totality of the publicly available evidence supports the effect of substituting corn oil for saturated fat and lowering of total and LDL cholesterol, thereby reducing the risk of CHD. Second, significant agreement exists among qualified experts that the relationship (PUFAs lowering total and LDL cholesterol, thereby reducing the risk of CHD) is valid as evidenced by the *2005 Dietary Guidelines* Advisory Committee Report (2005 DGAC 2004); the *2005 Dietary Guidelines for Americans*; the AHA Scientific Statement (Krauss et al. 2000); the Macronutrient Report (IOM 2002, 2002/2005); the WHO/FAO Report (2003); and the National Heart, Lung and Blood Institute's Expert Panel of the National Cholesterol Education Program in the Adult Treatment Panel III Report (NCEP 2002). Furthermore, FDA (1999) has stated that SSA is met when the validity of a substance/disease relationship is not likely to be reversed by new and evolving science, although the exact nature of the relationship may need to be refined over time. For almost 50 years, research results have remained constant concerning the positive effect of corn oil on CHD through the lowering of total and LDL cholesterol. This relationship is unlikely to be reversed by new and evolving science.

Chapter 5 REFERENCES

Reference Volume 1 of 9

SCIENTIFIC AND PUBLIC NUTRITION POLICY DOCUMENTS

2005 Dietary Guidelines Advisory Committee. Report of the *Dietary Guidelines* Advisory Committee on the *Dietary Guidelines for Americans, 2005.* 2004. http://www.health.gov/dietaryguidelines/dga2005/report/. Accessed 2/15/05.

American Dietetic Association. The American Dietetic Association's Evidence Analysis Process. Information Packet. *Prepared by* Patricia Splett. Evidence Analysis Workshop. January 27, 2003.

American Heart Association. *Heart Disease and Stroke Statistics –2006 Update.* Dallas, TX: American Heart Association; 2006. (Note: in volume 9) http://www.americanheart.org/downloadable/heart/1136308648540Statupdate2006.pdf

American Heart Association. *Heart Disease and Stroke Statistics –2005 Update.* Dallas, TX: American Heart Association; 2005. http://www.americanheart.org/downloadable/heart/1079736729696HDSStats2004UpdateREV3-19-04.pdf . Accessed 1/05.

FDA Task Force on Consumer Health Information for Better Nutrition, CFSAN. Task Force Report on Qualified Health Claims. July 2003. www.cfsan.fda.gov/~dms/nuttftoc.html. Accessed 3/10/05.

FDA, CFSAN. Letter Responding to Health Claim Petition dated August 28, 2003: Monounsaturated Fatty Acids from Olive Oil and Coronary Heart Disease (Docket No 2003Q-0559). November 2004. http:www.cfsan.fda.gov/~dms/qhcolive.html. Accessed 3/10/05.

FDA, CFSAN. Guidance for Industry Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements. December 1999. http:www.cfsan.fda.gov/~dms/ssaguide.html. Accessed 3/10/05.

FDA. Health Claims: Plant Sterol/Stanol Esters and Risk of Coronary Heart Disease. 21 CFR § 101.83.

FDA. Health Claims: Dietary Saturated Fat and Cholesterol and Risk of Coronary Heart Disease. 21 CFR § 101.75.

FMI, PREVENTION and Rodale Inc. Shopping for Health 2004: Making Sense of Nutrition News & Health Claims. Food Marketing Institute: Washington, DC, 2004.

Joint WHO/FAO Consultation on Diet, Nutrition and the Prevention of Chronic Diseases. Diet, Nutrition and the Prevention of Chronic Diseases: Report of a Joint WHO/FAO Expert Consultation. WHO Technical Report Series; 916). WHO: Geneva, Switzerland, 2003.

Reference Volume 2 of 9

Krauss et al. (2000). The American Heart Association Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update. Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients without Coronary or Other Atherosclerotic Vascular Diseases. Circulation. 2002; 106:388-391.

National Cholesterol Education Program (NCEP), National Heart Lung and Blood Institute, National Institutes of Health. Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). NIH Publication No. 02-5215. 2002 http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm. Accessed 1/10/05.

Nutrition Labeling and Education Act 1990.
http://www.access.gpo.gov/uscode/title21/chapter9_subchapteriv_.html. Pub L No. 101-535, 104 Stat 2353. http://www.access.gpo.gov/uscode/title21/chapter9_subchapteriv_.html. or http://www.fda.gov/opacom/laws/. or http://www.fda.gov/ora/inspect_ref/igs/nleatxt.html. Accessed 6/10/04.

Reference Volume 3 of 9

Panel on Macronutrients, Panel on the Definition of Dietary Fiber, Subcommittee on Upper Reference Levels of Nutrients, Subcommittee on Interpretation and Uses of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Food and Nutrition Board. Institute of Medicine of the National Academies. Dietary References Intakes: Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids (Macronutrient Report). The National Academy Press: Washington, DC, 2002/2005. (Note: in volume 9)

Panel on Macronutrients, Panel on the Definition of Dietary Fiber, Subcommittee on Upper Reference Levels of Nutrients, Subcommittee on Interpretation and Uses of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Food and Nutrition Board. Institute of Medicine of the National Academies. Dietary References Intakes: Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids (Macronutrient Report). The National Academy Press: Washington, DC, 2002

U.S. Department of Agriculture, Agricultural Research Service. 2004. USDA National Nutrient Database for Standard Reference, Release 17. Nutrient Data Laboratory Home Page, http://www.ars.usda.gov/main/site_main.htm?modecode=12354500. Accessed 4/12/06.

US Department of Health and Human Services (USDHHS) and US Department of Agriculture (USDA) and Dietary Guidelines for Americans 2005 . www.healthierus.gov/dietaryguidelines. Accessed 1/20/05.

US Department of Agriculture (USDA) and US Department of Health and Human Services (USDHHS). Dietary Guidelines for Americans 2000. 5th ed. USDA Home and Garden Bulletin No. 232, 2000.

US Department of Agriculture Economic Research Services. Last updated December 21, 2004. http://www.ers.usda.gov/data/foodconsumption/FoodAvailSpreadsheets.htm#fats. Accessed April 5, 2005.

CORN OIL: EFFECT ON BLOOD LIPIDS

DESIGN TYPE 1: RANDOMIZED, CONTROLLED, INTERVENTION TRIALS

Childs MT, Bowlin JA, Ogilvie JT, Hazzard WR, Albers JJ. The contrasting effects of a dietary soya lecithin product and corn oil on lipoprotein lipids in normolipidemic and familial hypercholesterolemic subjects. Atherosclerosis. 1981;Jan-Feb;38(1-2):217-28.

Dayton S. Pearce ML, Hashimoto S, Dixon WJ, Tomiyasu U. A controlled clinical trial of a diet high in unsaturated fat in preventing complications of atherosclerosis. Circulation. 1969;40:1-63.

Grundt H, Nilsen DW, Hetland O, Mansoor MA. Clinical outcome and atherothrombogenic risk profile after prolonged wash-out following long-term treatment with high doses of n-3 PUFAs in patients with an acute myocardial infarction. Clin Nutr. 2004 Aug;23(4):491-500.

Hiscock E, Dayton S, Pearce ML, Hashimoto S. A palatable diet high in unsaturated fat. J Am Diet Assoc. 1962 May;40:427-31.

Howell TJ, MacDougall DE, Jones PJH. Phytosterols partially explain differences in cholesterol metabolism caused by corn or olive oil feeding. J Lipid Res. 1998 Apr;39(4):892-900.

Insull W Jr, Silvers A, Hicks L, Probstfield JL. Plasma lipid effects of three common vegetable oils in reduced-fat diets of free-living adults. Am J Clin Nutr. 1994 Aug;60(2):195-202.

Jones PJH, Lichtenstein AH, Schaefer EJ, Namchuk GL. Effect of dietary fat selection on plasma cholesterol synthesis in older, moderately hypercholesterolemic humans. Arterioscler Thromb. 1994 Apr;14(4):542-8.

Kohlmeier M, Riesen W, Schlierf G. Metabolic changes in healthy men using fat-modified diets. I. Disposition of serum cholesterol. Ann Nutr Metab. 1988;32(1):1-9.

Laine DC, Snodgrass CM, Dawson EA, Ener MA, Kuba K, Frantz ID Jr. Lightly hydrogenated soy oil versus other vegetable oils as a lipid-lowering dietary constituent. Am J Clin Nutr. 1982 Apr;35(4):683-90.

Lichtenstein AH, Ausman LM, Carrasco W, Gualtieri LJ, Jenner JL, Ordovas JM, Nicolosi RJ, Goldin BR, Schaefer EJ. Rice bran oil consumption and plasma lipid levels in moderately hypercholesterolemic humans. Arterioscler Thromb. 1994a Apr;14(4):549-56.

Lichtenstein AH, Ausman LM, Carrasco W, Jenner JL, Ordovas JM, Schaefer EJ. Hypercholesterolemic effect of dietary cholesterol in diets enriched in polyunsaturated and saturated fat. Dietary cholesterol, fat saturation, and plasma lipids.
Arterioscler Thromb. 1994b Jan;14(1):168-75.

Lichtenstein AH, Ausman LM, Carrasco W, Jenner JL, Ordovas JM, Schaefer EJ. Hydrogenation impairs the hypolipidemic effect of corn oil in humans. Hydrogenation, *trans* fatty acids, and plasma lipids. Arterioscler Thromb. 1993a Feb;13(2):154-61.

Lichtenstein AH, Ausman LM, Carrasco W, Jenner JL, Gualtieri LJ, Goldin BR, Ordovas JM, Schaefer EJ. Effects of canola, corn, and olive oils on fasting and postprandial plasma lipoproteins in humans as part of a National Cholesterol Education Program Step 2 diet. Arterioscler Thromb. 1993b Oct;13(10):1533-42.

Ng TKW, Hassan K, Lim JB, Lye MS, Ishak R. Nonhypercholesterolemic effects of a palm-oil diet in Malaysian volunteers. Am J Clin Nutr. 1991 Apr;53(4 Suppl):1015S-1020S.

Rose GA, Thomson WB, Williams RT. Corn oil in treatment of ischaemic heart disease. Br Med J. 1965 Jun 12;544:1531-3.

Schwab US, Ausman LM, Vogel S, Li Z, Lammi-Keefe CJ, Goldin BR, Ordovas JM, Schaefer EJ, Lichtenstein AH. Dietary cholesterol increases the susceptibility of low density lipoprotein to oxidative modification. Atherosclerosis. 2000 Mar;149(1):83-90.

Schwab US, Vogel S, Lammi-Keefe CJ, Ordovas JM, Schaefer EJ, Li Z, Ausman LM, Gualtieri L, Goldin BR, Furr HC, Lichtenstein AH. Varying dietary fat type of reduced-fat diets has little effect on the susceptibility of LDL to oxidative modification in moderately hypercholesterolemic subjects. J Nutr. 1998 Oct;128(10):1703-9.

Sirtori CR, Gatti E, Tremoli E, Galli C, Gianfranceschi G, Franceschini G, Colli S, Maderna P, Marangoni F, Perego P, Stragliotto E. Olive oil, corn oil, and n-3 fatty acids differently affect lipids, lipoproteins, platelets, and superoxide formation in type II hypercholesterolemia. Am J Clin Nutr. 1992 Jul;56(1):113-22.

Sirtori CR, Tremoli E, Gatti E, Montanari G, Sirtori M, Colli S, Gianfranceschi G, Maderna P, Dentone CZ, Testolin G, Galli C. Controlled evaluation of fat intake in the Mediterranean diet: comparative activities of olive oil and corn oil on plasma lipids and platelets in high-risk patients. Am J Clin Nutr. 1986 Nov;44(5):635-42.

Wagner K-H, Tomasch R, Elmadfa I. Impact of diets containing corn oil or olive/sunflower oil mixture on the human plasma and lipoprotein lipid metabolism. Eur J Nutr. 2001 Aug;40(4):161-7.

Wardlaw GM, Snook JT. Effect of diets high in butter, corn oil, or high-oleic acid sunflower oil on serum lipids and apolipoproteins in men. Am J Clin Nutr. 1990 May;51(5):815-21.

Reference Volume 5 of 9

DESIGN TYPE 3: NONRANDOMIZED, INTERVENTION TRIALS WITH CONCURRENT OR HISTORICAL CONTROLS AND CASE-CONTROL STUDIES

Chance GW, Albutt EC, Edkins SM. Control of hyperlipidaemia in juvenile diabetes. Standard and corn-oil diets compared over a period of 10 years. Br Med J. 1969 Sep;3(671):616-18.

Cuchel M, Schwab US, Jones PJH, Vogel S, Lammi-Keefe C, Li Z, Ordovas J, McNamara JR, Schaefer EJ, Lichtenstein AH. Impact of hydrogenated fat consumption on endogenous cholesterol synthesis and susceptibility of low-density lipoprotein to oxidation in moderately hypercholesterolemic individuals. Metabolism. 1996 Feb;45(2):241-7.

Engelberg H. Studies of serum cholesterol and low-density lipoprotein levels, previously lowered by a reduced fat intake, after the addition of corn oil to the diet. J Chronic Dis. 1957 Sep;6(3):229-33.

Fisher EA, Blum CB, Zannis VI, Breslow JL. Independent effects of dietary saturated fat and cholesterol on plasma lipids, lipoproteins, and apolipoprotein E. J Lipid Res. 1983 Aug;24(8):1039-48.

Grande F, Anderson JT, Keys A. Serum cholesterol in man and the unsaponifiable fraction of corn oil in the diet. Proc Soc Exp Biol Med. 1958 Jun;98(2):436-40.

Haust HL, Beveridge JM. Type and quantity of 3 β-hydroxysterols excreted by subjects subsisting on formula rations high in corn oil. J Nutr. 1963 Sep;81:13-1.

Horlick L. Studies on the regulation of serum-cholesterol levels in man. The effects of corn oil, ethyl stearate, hydrogenated soybean oil, and nicotinic acid when added to a very low-fat basal diet. Lab Invest. 1959 May-Jun;8(3):723-35.

Imaki M, Miyoshi T, Tanada S, Nakamura T, Yamada Y, Yamasaki R, Terada H. Effect of lard and corn oil intake on serum lipids in young men. Acta Biol Hung. 1989;40(3):271-82.

Kaplan BM, Spellberg MA, Norton MM, Pick R. Effect on serum cholesterol of a corn oil and skim milk mixture in peptic ulcer patients. Am J Med Sci. 1965 Dec;250(6):621-8.

Kingsbury KJ, Aylott C, Morgan DM, Emmerson R. Effects of ethyl arachidonate, cod-liver oil, and corn oil on the plasma-cholesterol level. A comparison in normal volunteers. Lancet. 1961 Apr; 1:739-41.

Lloyd JK, Fosbrooke AS, Wolff OH, Salt HB. Effect of dietary corn oil on lipaemia in diabetic children. Lancet. 1962 Jun;1:1329-30.

Mitchell DC, McMahon KE, Shively CA, Apgar JL, Kris-Etherton PM. Digestibility of cocoa butter and corn oil in human subjects: a preliminary study. Am J Clin Nutr. 1989 Nov;50(5):983-6.

Rhoads DV, Barker NW. Effect of reduction of dietary fat and additional ingestion of corn oil on hypercholesterolemia. Mayo Clin Proc. 1959 Apr;34(9):225-9.

Snook JT, DeLany JP, Vivian VM. Effect of moderate to very low fat defined formula diets on serum lipids in healthy subjects. Lipids. 1985 Nov;20(11):808-16.

Tobian L, Tuna N. The efficacy of corn oil in lowering serum cholesterol of patients with coronary atherosclerosis. Am J Med Sci. 1958 Feb;235(2):133-7.

Watson WC. Long-term administration of corn oil in management of patients after myocardial infarction: a four-year study. Br Med J. 1963 Nov;5369:1366-9.

Zanni EE, Zannis VI, Blum CB, Herbert PN, Breslow JL. Effect of egg cholesterol and dietary fats on plasma lipids, lipoproteins, and apoproteins of normal women consuming natural diets. J Lipid Res. 1987 May;28(5):518-27.

DESIGN TYPE 4: CROSS-SECTIONAL STUDIES, ANALYSES OF SECONDARY DISEASE ENDPOINTS IN INTERVENTION TRIALS AND CASE SERIES

Albutt EC, Chance GW. Fasting plasma cholesteryl esters in diabetic children consuming corn oil. Am J Clin Nutr. 1969 Dec;22(12):1552-4.

Carlson LA, Sterner G. Essential hypercholesterolaemia in two siblings. Effect of corn oil on serum-lipids. Acta Paediatr. 1960 Mar;49:168-74.

META-ANALYSES AND SYSTEMATIC REVIEWS

Dupont J, White PJ, Carpenter MP, Schaefer EJ, Meydani SN, Elson CE, Woods M, Gorbach SL. Food uses and health effects of corn oil. J Am Coll Nutr. 1990 Oct;9(5):438-70.

Reference Volume 6 of 9

ANIMAL STUDIES

Anonymous. Corn oil and plasma cholesterol. Nutr Rev. 1958 Mar;16(3):83-4.

Day AJ. The effect of corn oil and of coconut oil on the esterification and removal of cholesterol by reticulo-endothelial cells. Aust J Exp Biol Med Sci. 1960 Dec;38:461-6.

Ramjiganesh T, Roy S, Freake HC, McIntyre JC, Fernandez ML. Corn fiber oil lowers plasma cholesterol by altering hepatic cholesterol metabolism and up-regulating LDL receptors in guinea pigs. J Nutr. 2002 Mar;132(3):335-40.

EFFECT OF PHYTOSTEROLS, DESIGN TYPE 1, DESIGN TYPE 3 AND ANALYTICAL STUDIES

Grande F, Anderson JT, Keys A. Serum cholesterol in man and the unsaponifiable fraction of corn oil in the diet. Proc Soc Exp Biol Med. 1958 Jun;98(2):436-40.

Haust HL, Beveridge JM. Type and quantity of 3 β-hydroxysterols excreted by subjects subsisting on formula rations high in corn oil. J Nutr. 1963 Sep;81:13-16.

Howell TJ, MacDougall DE, Jones PJH. Phytosterols partially explain differences in cholesterol metabolism caused by corn or olive oil feeding. J Lipid Res. 1998 Apr;39(4):892-900.

Kohlmeier M, Riesen W, Schlierf G. Metabolic changes in healthy men using fat-modified diets. I. Disposition of serum cholesterol. Ann Nutr Metab. 1988;32(1):1-9.

Milkova T, Popov A, Selva A, Vettori U. Sterol composition of Bulgarian soya and corn oils. Nahrung. 1977;21(1):7-12.

Moreau RA, Hicks KB, Powell MJ. Effect of heat pretreatment on the yield and composition of oil extracted from corn fiber. J Agric Food Chem. 1999 Jul;47(7):2869-71.

Ostlund RE Jr, Racette SB, Okeke A, Stenson WF. Phytosterols that are naturally present in commercial corn oil significantly reduce cholesterol absorption in humans. Am J Clin Nutr. 2002 Jun;75(6):1000-4.

Wagner K-H, Tomasch R, Elmadfa I. Impact of diets containing corn oil or olive/sunflower oil mixture on the human plasma and lipoprotein lipid metabolism. Eur J Nutr. 2001 Aug;40(4):161-7.

EFFECTS ON ATHEROGENICITY/OXIDATIVE MODIFICATION OF LDL, DESIGN TYPE 1 AND DESIGN TYPE 3 STUDIES

Cuchel M, Schwab US, Jones PJH, Vogel S, Lammi-Keefe C, Li Z, Ordovas J, McNamara JR, Schaefer EJ, Lichtenstein AH. Impact of hydrogenated fat consumption on endogenous cholesterol synthesis and susceptibility of low-density lipoprotein to oxidation in moderately hypercholesterolemic individuals. Metabolism. 1996 Feb;45(2):241-7.

Schwab US, Ausman LM, Vogel S, Li Z, Lammi-Keefe CJ, Goldin BR, Ordovas JM, Schaefer EJ, Lichtenstein AH. Dietary cholesterol increases the susceptibility of low density lipoprotein to oxidative modification. Atherosclerosis. 2000 Mar;149(1):83-90.

Schwab US, Vogel S, Lammi-Keefe CJ, Ordovas JM, Schaefer EJ, Li Z, Ausman LM, Gualtieri L, Goldin BR, Furr HC, Lichtenstein AH. Varying dietary fat type of reduced-fat diets has little effect on the susceptibility of LDL to oxidative modification in moderately hypercholesterolemic subjects. J Nutr. 1998 Oct;128(10):1703-9.

POSTPRANDIAL EFFECTS ON BLOOD LIPIDS, DESIGN TYPE 1 AND DESIGN TYPE 3 STUDIES

Muesing RA, Griffin P, Mitchell P. Corn oil and beef tallow elicit different postprandial responses in triglycerides and cholesterol, but similar changes in constituents of high-density lipoprotein. J Am Coll Nutr. 1995 Feb;14(1):53-60.

Schlierf G, Jessel S, Ohm J, Heuck CC, Klose G, Oster P, Schellenberg B, Weizel A. Acute dietary effects on plasma lipids, lipoproteins and lipolytic enzymes in healthy normal males. Eur J Clin Invest. 1979 Oct;9(5):319-25.

Tall AR, Blum CB, Forester GP, Nelson CA. Changes in the distribution and composition of plasma high density lipoproteins after ingestion of fat. J Biol Chem. 1982 Jan;257(1):198-207.

Zampelas A, Peel AS, Gould BJ, Wright J, Williams CM. Polyunsaturated fatty acids of the *n*-6 and n-3 series: effects on postprandial lipid and apolipoprotein levels in healthy men. Eur J Clin Nutr. 1994 Dec;48(12):842-8.

Reference Volume 7 of 9

PUFAS AND CHD/CVD

DESIGN TYPE 1: RANDOMIZED, CONTROLLED, INTERVENTION TRIALS

Becker N, Illingworth DR, Alaupovic P, Connor WE, Sundberg EE. Effects of saturated, monounsaturated and ω-6 polyunsaturated fatty acids on plasma lipids, lipoproteins and apoproteins in humans. Am J Clin Nutr. 1983 Mar;37:355-60.

Howard BV, Hannah JS, Heiser CC, Jablonski KA, Paidi MC, Alarif L, Robbins DC, Howard WJ. Polyunsaturated fatty acids result in greater cholesterol lowering and less triacylglycerol elevation than do monounsaturated fatty acids in a dose-response comparison in a multiracial study group. Am J Clin Nutr. 1995; 62:392-402.

Kris-Etherton PM, Derr J, Mitchell DC, Mustad VA, Russell ME, McDonnell ET, Salabsky D, Pearson TA. The role of fatty acid saturation on plasma lipids, lipoproteins and apolipoproteins: I. Effects of whole food diets high in cocoa butter, olive oil, soybean oil, dairy butter, and milk chocolate on the plasma lipids of young men. Metabolism. 1993 Jan;42:121-9.

Mattson FH, Grundy SM. Comparison of effects of dietary saturated, monounsaturated, and polyunsaturated fatty acids on plasma lipids and lipoproteins in man. J Lipid Res. 1985;26:194-202.

McDonald BE, Gerrard JM, Bruce VM, Corner EJ. Comparison of the effect of canola oil and sunflower oil on plasma lipids and lipoproteins and on in vivo thromboxane A2 and prostacyclin production in healthy young men. Am J Clin Nutri. 1989 Dec;50:1382-8.

Zock PL, Katan MB. Hydrogenation alternatives: effects of *trans* fatty acids and stearic acid versus linoleic acid on serum lipids and lipoproteins in humans. J Lipid Res. 1992;33:399-410.

DESIGN TYPE 2: PROSPECTIVE, OBSERVATIONAL, COHORT STUDIES

Ascherio A, Rimm EB, Giovannucci EL Spiegelman D, Stampher M, Willett WC. Dietary fat and risk of coronary heart disease in men: cohort follow up study in the United States. BMJ. 1996 Jul; 313:84-90.

Hu FB, Stampfer MJ, Manson JE, Rimm E, Colditz GA, Rosner BA, Hennekens CH, Willett WC. Dietary fat intake and the risk of coronary heart disease in women. N Eng J Med. 1997;337:1491-9.

Keys, A .Nutrition. 1997 Mar;13(3):252-3 (Note: Includes Keys A. Coronary heart disease in Seven Countries). Circulation. 1970 April;41(suppl1):251-3.

Kromhout D, Menotti A, Bloemberg B, Aravanis C, Blackburn H, Buzina R, Dontas AS, Fidanza F, Giampaoli S, Jansen A, et al. Dietary saturated and *trans* fatty acids and cholesterol and 25-year mortality from coronary heart disease: the Seven Countries Study. Prev Med. 1995;24:308-15.

Laaksonen DE, Nyyssõnen K, Niskanen L, Rissanen TH, Salonen JT. Prediction of cardiovascular mortality in middle-aged men by dietary and serum linoleic and polyunsaturated fatty acids. Arch Intern Med. 2005 Jan;165:193-99.

Posner BM, Cobb JL, Belanger AJ, Cupples LA, D'Agostino RB, Stokes J III. Dietary lipid predictors of coronary heart disease in men. The Framingham Study. Arch Intern Med.1991 Jun;151:1181-7.

Shekelle RB, Shryock AM, Paul O, Lepper M, Stamler J, Liu S, Raynor WJ Jr. Diet, serum cholesterol, and death from coronary heart disease. The Western Electric Study. N Engl J Med.1981 Jan; 304(2):65-70.

DESIGN TYPE 3: NONRANDOMIZED, INTERVENTION TRIALS WITH CONCURRENT OR HISTORICAL CONTROLS AND CASE-CONTROL STUDIES

Artaud-Wild SM, Connor SL, Sexton G, Connor WE. Lipids/atherosclerosis/arteries: differences in coronary mortality can be explained by differences in cholesterol and saturated fat intakes in 40 countries but not in France and Finland. A paradox. Circulation. 1993 Dec; 88:2771-9.

Garcia-Palmieri MR, Sorlie P, Tillotson J, Costas R Jr, Cordero E, Rodriguez M. Relationship of dietary intake to subsequent coronary heart disease incidence: the Puerto Rico Heart Health Program. Am J Clin Nutr. 1980 Aug; 33:1818-27.

Gordon T, Kagan A, Garcia-Palmieri M, Kannel WB, Zukel WJ, Tillotson J, Sorlie P, Hjortland M. Diet and its relation to coronary heart disease and death in three populations. Circulation. 1981;63(3):500-15.

Hegsted DM and Ausman LM. Diet, alcohol and coronary heart disease in men. J Nutr. 1988;118:1184-9.

Joossens JV, Geboers J, Kesteloot H. Nutrition and cardiovascular mortality in Belgium. For the B.I.R.N.H. Study Group. Acta Cardiol. 1989;44(2):157-82.

Kark JD, Kaufmann NA, Binka F, Goldberger N, Berry EM, Adipose tissue *n*-6 fatty acids and acute myocardial infarction in a population consuming a diet high in polyunsaturated fatty acids. Am J Clin Nutr. 2003;77:796 -802.

Keys A, Anderson JT, Grande F. Prediction of serum-cholesterol responses of man to changes in fats in the diet. Lancet. 1957 Nov; 273(7003):959-66.

Kushi LH, Lew RA, Stare FJ, Ellison CR, el Lozy M, Bourke G, Daly L, Graham I, Hickey N, Mulcahy R, Kevaney J. Diet and 20-year mortality from coronary heart disease. The Ireland-Boston Diet-Heart Study. N Engl J Med.1985 Mar; 312(13):811-8.

Tell GS, Evans GW, Folsom AR, Shimakawa T, Carpenter MA, Heiss G. Dietary fat intake and carotid artery wall thickness: the Atherosclerosis Risk in Communities (ARIC) Study. Am J Epidemiol. 1994;139(10):979-89.

<u>Reference Volume 8 of 9</u>

DESIGN TYPE 4: CROSS-SECTIONAL STUDIES, ANALYSES OF SECONDARY DISEASE ENDPOINTS IN INTERVENTION TRIALS AND CASE SERIES

Djoussé L, Pankow JS, Eckfeldt JH, Folsom AR, Hopkins PN, Province MA, Hong Y, Ellison RC. Relation between dietary linolenic acid and coronary artery disease in the National Heart, Lung, and Blood Institute Family Heart Study. Am J Clin Nutr. 2001 Nov;74(5):612-9.

REVIEWS

Hu FB, Manson JE, Willett WC. Types of dietary fat and risk of coronary heart disease: a critical review. J Am Coll Nutr. 2001;20:5-19.

Hu FB, Willett WC. Optimal diets for prevention of coronary heart disease. J Am Med Assoc. 2002 Nov;288(20):2569-78.

Kris-Etherton P. Hecker KD, Binkoski AE. Polyunsaturated fatty acids and cardiovascular health. Nutr Rev. 2004;62(11):414-26.

Mock DC Jr. Coronary disease, cholesterol, corn oil and confusion. J Okla State Med Assoc. 1959 Feb;52(2):79-85.

Sacks FM, Katan M. Randomized clinical trials on the effects of dietary fat and carbohydrate on plasma lipoproteins and cardiovascular disease. Am J Med. 2002 Dec;113(913):13S-24S.

ANIMAL STUDIES

Rudel LL, Haines J, Sawyer JK, Shah R, Wilson MS, Carr TP. Hepatic origin of cholesteryl oleate in coronary artery atherosclerosis in African green monkeys. Enrichment by dietary monounsaturated fat. J Clin Invest. 1997 Jul;100(1):74-83.

Rudel LL, Parks JS, Sawyer JK. Compared with dietary monounsaturated and saturated fat, polyunsaturated fat protects African green monkeys from coronary artery atherosclerosis. Arterioscler Thromb Vasc Biol. 1995a Dec;15(12):2101-10.

Rudel LL, Johnson FL, Sawyer JK, Wilson MS, Parks JS. Dietary polyunsaturated fat modifies low-density lipoproteins and reduces atherosclerosis of nonhuman primates with high and low diet responsiveness. Am J Clin Nutr. 1995b Aug;62(2):463S-70S.

Wolfe MS, Sawyer JK, Morgan TM, Bullock BC, Rudel LL.. Dietary polyunsaturated fat decreases coronary artery atherosclerosis in a pediatric-aged population of African green monkeys. Arterioscler Thromb. 1994 Apr;14(4):587-97.

ADDITIONAL CITATIONS

Allison DB, Egan K, Barraj LM, Caughman C, Infante M, Heimbach JT. Estimated intakes of *trans* fatty and other fatty acids in the US population. J Am Diet Assoc. 1999;99:166-74.

Kojima M, Wakai K, Tokudome S, Suzuki K, Tamakoshi K, Watanabe Y, Kawado M, Hashimoto S, Hayakawa N, Ozasa K, Hideaki T, Suzuki S, Ito Y, Tamakoshi A, for the JACC Study Group. Serum levels of polyunsaturated fatty acids and risk of colorectal cancer: a prospective study. Am J Epidemiol. 2005;161(5):462-71.

Troiano RP, Briefel RR, Carroll MD, Bialostosky K. Energy and fat intakes of children and adolescents in the United States: data from the National Health and Nutrition Examination Surveys. Am J Clin Nutr. 2000; 72(Suppl):1343S – 53S.

<u>*Reference Volume 9 of 9*</u>

American Heart Association. *Heart Disease and Stroke Statistics –2006 Update.* Dallas, TX: American Heart Association; 2006.
http://www.americanheart.org/downloadable/heart/1136308648540Statupdate2006.pdf

Panel on Macronutrients, Panel on the Definition of Dietary Fiber, Subcommittee on Upper Reference Levels of Nutrients, Subcommittee on Interpretation and Uses of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Food and Nutrition Board. Institute of Medicine of the National Academies. Dietary References Intakes: Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids (Macronutrient Report). The National Academy Press: Washington, DC, 2002/2005.

Phillips KM , Ruggio DM, Toivo JI, Swank MA, Simpkins. Free and esterified sterol composition of edible oils and fats. J Food Comp Anal. 2002;15:123-42.